Global Medical Safety,
Janssen Research & Development, LLC
850 Ridgeview Drive
Horsham, Pennsylvania, 19044
USA

Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report

OROS® Methylphenidate Hydrochloride

Note: This report contains unblinded clinical trial adverse event data

PERIOD COVERED BY THIS REPORT:
11 October 2012 to 31 October 2013

INTERNATIONAL BIRTH DATE:
01 August 2000

COUNTRY OF FIRST REGISTRATION:
United States

Report Date: 23 December 2013
Department: Global Medical Safety
Document No.: EDMS-ERI-70003049:1.0

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you that is indicated as *privileged or confidential*.

APPROVER CREDENTIALS

Name and Contact Details of the EEA QPPV Pharma:

[redacted]

Therapeutic Area Safety Head:

[redacted]

AR Scientist:

[redacted]

GMS Physician:

I have reviewed this report and confirm that, to the best of my knowledge, it accurately describes the data available to date:

[redacted]

Electronic signatures have been applied at the end of the report.

EXECUTIVE SUMMARY

Introduction

This Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) for OROS® methylphenidate hydrochloride, marketed as CONCERTA® summarises the safety data obtained by the Company from worldwide sources for the reporting period of 11 October 2012 to 31 October 2013. The content and format of this report follows International Conference on Harmonisation E2C guidelines on the PBRER and Module VII of the Guideline on Good Pharmacovigilance Practices on the PSUR. This is the first PBRER/PSUR covering OROS methylphenidate hydrochloride. The first approval of OROS methylphenidate hydrochloride was in the United States on 01 August 2000. The registered formulation of OROS methylphenidate hydrochloride is a prolonged-release tablet, and it is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (See Section 1, Introduction).

Worldwide Marketing Approval Status

OROS methylphenidate hydrochloride is authorised in 89 countries worldwide (See Section 2, Worldwide Marketing Authorisation Status).

Exposure

Cumulative Exposure in Clinical Trials

The clinical development for OROS methylphenidate hydrochloride was initiated 20 years ago. Since that time, OROS methylphenidate hydrochloride has been studied in numerous Company-sponsored trials. Due to the maturity of the product, in terms of its clinical development, a reliable, precise estimate of subjects exposed in all Company-sponsored clinical trials with OROS methylphenidate hydrochloride is not available. In this respect, however, the subject exposures in 7 placebo-controlled, or active-controlled, double-blind clinical trials, and 20 open-label clinical trials of OROS methylphenidate hydrochloride are described in Section "Adverse Reactions" of the CCDS. Approximately 4,428 patients were treated with OROS methylphenidate in these trials (See Section 5.1, Cumulative Subject Exposure in Clinical Trials).

Cumulative and Interval Patient Exposure from Marketing

Based on the [redacted] tablets of OROS methylphenidate hydrochloride distributed (from 01 October 2012 to 31 October 2013), the estimated exposure is [redacted] person-months or [redacted] person-years. Based on the [redacted] tablets of OROS methylphenidate hydrochloride distributed by the company (from launch to 31 October 2013), the estimated exposure is [redacted] person-months or [redacted] person-years (See Section 5.2, Cumulative and Interval Patient Exposure from Marketing Experience).

Summary of the Overall Benefit-Risk Analysis Evaluation

OROS methylphenidate hydrochloride is an effective treatment for Attention Deficit Hyperactivity Disorder. The benefit is maintained over the 1-year period studied. The impact on patients' lives is in both clinical measurements (efficacy endpoints) and quality of life assessments. The important potential risks tend to occur with similar frequency in patients with Attention Deficit Hyperactivity Disorder.

The post-marketing safety data of OROS methylphenidate hydrochloride remains favourable. There are no new safety data available during this period that have meaningfully altered the overall benefit risk profile for the approved indication. The benefit-risk balance remains positive (See Section 18.2, Benefit-Risk Analysis Evaluation).

Actions Taken and Proposed for Safety Reasons

The following actions were taken during the PBRER/PSUR period:

European Union:

On 23 July 2007, the Committee for Medicinal Products for Human Use initiated an Article 31 referral procedure for all marketing authorisation holders of methylphenidate-containing products in the European Union. This was due to concerns about cardiovascular adverse events including sudden death; cerebrovascular disorders; and psychiatric disorders. Following discussions between the Committee for Medicinal Products for Human Use and marketing authorisation holders, the Rapporteur's (Medicines and Healthcare Products Regulatory Agency) Final Assessment Report was issued on 03 December 2008. A final opinion was issued on 22 January 2009. The Committee for Medicinal Products for Human Use did not restrict use of methylphenidate-containing products, but required the addition of pre-treatment screening and ongoing monitoring instructions to the prescribing information. A number of post-referral commitments for marketing authorisation holders of methylphenidate containing products were also adopted by the Committee for Medicinal Products for Human Use. The Committee for Medicinal Products for Human Use opinion was ratified by the European Commission on 27 May 2009.

The following status update for the European Union Article 31 referral commitments provides a summary of the outstanding actions that have been taken or were in progress during the current reporting period by the Company (and marketing authorisation holders) to fulfil the Conditions of the Marketing Authorisations as adopted by the Committee for Medicinal Products for Human Use (Annex IV of European Commission decision; Appendix 2), hereafter referred to as 'conditions':

Sexual Maturation

As part of the European Union Article 31 referral conditions, the marketing authorisation holders were requested to make available the final study report of an Investigator Initiated Study using Tanner staging examinations to evaluate effects of methylphenidate on sexual maturation. A copy of the manuscript from the Investigator Initiated Study was submitted to the Medicines and Healthcare Products Regulatory Agency on 12 September 2012 for information confirming the study findings that long term treatment with OROS methylphenidate does not have a detrimental effect on sexual maturation in adolescents with Attention Deficit Hyperactivity Disorder.

As the manuscript has not yet been accepted for publication, the marketing authorisation holders consider the submission of the manuscript on 12 September 2012 as fulfilment of this condition. Should the manuscript be published in the future, then the Company will forward the report to the Medicines and Healthcare Products Regulatory Agency for review.

Drug utilisation

As part of the European Union Article 31 referral conditions, the marketing authorisation holders were requested to submit annual drug utilisation data for 5 consecutive years to allow an evaluation of changes in usage over time. The Company (with other marketing authorisation holders) provides on an annual basis all available retrospective drug utilisation data using health related electronic databases in all European Union Member States (and additionally Switzerland) where methylphenidate is used and to the extent such databases are available. An evaluation of methylphenidate usage in 2012 will be included in the PSUR workshare submission in the European Union (UK/H/PSUR/0068/005), to be submitted in December 2013. This drug utilisation study represents the fifth and final drug utilisation study to address the Article 31 referral commitment for a drug utilisation study, which only requested retrospective data on an annual review basis for 5 years.

Educational tools

As part of the European Union Article 31 referral conditions, the marketing authorisation holders were requested to produce fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklists) containing all of the important information from the Clinical Particulars section of the European core Summary of Product Characteristics for assessment. The Medicines and Healthcare Products Regulatory Agency requested further changes in its Risk Management Plan Final Assessment

Report of September 2010. The marketing authorisation holders addressed the issues raised by the Medicines and Healthcare Products Regulatory Agency and other Concerned Member States within the submission package to support UK/H/PSUR/0068/002, submitted 09 December 2010. In Medicines and Healthcare Products Regulatory Agency's Risk Management Plan Final Assessment Report of 26 September 2012, the Medicines and Healthcare Products Regulatory Agency confirmed the educational tools could progress to the 'national phase' and that the marketing authorisation holders should proceed with obtaining national agreement of texts to obtain endorsement and allow the implementation of the tools on a per country basis.

At time of writing, approval of the educational tools has been received in the following Member States: Ireland (19 February 2013), Malta (10 October 2013), Norway (21 November 2013), Romania (24 November 2013), Spain (22 November 2013), and UK (19 September 2013). The educational tools have been submitted in the following Member States: Belgium, Bulgaria, Estonia, Greece, Iceland, Italy, Lithuania, the Netherlands, Poland and Slovakia.. Submission to national Health Authorities will continue into 2014.

Medicines and Healthcare Products Regulatory Agency Request for marketing authorisation holders to Further Investigate Signals for Spina Bifida/Neural Tube Defects from the World Health Organisation Collaborating Centre for the European Surveillance of Congenital Anomalies.

In the 26 September 2012 Work sharing PSUR Final Assessment Report, the Medicines and Healthcare Products Regulatory Agency requested the marketing authorisation holders to address the following point in the next PSUR:

"The marketing authorisation holders are requested to obtain and evaluate data to further investigate the signal for spina bifida/neural tube defects from the World Health Organisation Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies."

In September 2012 a request was made to the Centre for the Epidemiological Surveillance of Congenital Anomalies for information on cases of spina bifida/neural tube defects associated with the use of methylphenidate products in order to identify trends or potential clusters related with the methylphenidate exposure. The following information together with the listed caveats was provided by Centre for the Epidemiological Surveillance of Congenital Anomalies on 22 October 2012:

"There are 5 cases with maternal exposure to methylphenidate (N06BA04) in the Centre for the Epidemiological Surveillance of Congenital Anomalies database, for the years 1995-2010.

Please note the following important caveats:

- At present, the 5 cases of methylphenidate exposure have not been confirmed by the contributing registries.
- Not all medication exposures are recorded by Centre for the Epidemiological Surveillance of Congenital Anomalies registries.
- This should not be interpreted as the prevalence of exposed cases of congenital anomaly in the European population. It is only a guide as to whether a study using the Centre for the Epidemiological Surveillance of Congenital Anomalies database to identify any specific malformation associated with exposure is feasible."

Further details regarding the 5 cases was requested (the type of neural tube defect experienced, the methylphenidate product (if known), concomitant medication, etc.). The Centre for the Epidemiological Surveillance of Congenital Anomalies confirmed it was presently reviewing its internal medication data request procedures and could not provide additional information on the 5 cases until 2013. Janssen submitted a medication enquiry to Centre for the Epidemiological Surveillance of Congenital Anomalies in October 2013 and currently awaits a reply.

Outstanding commitments for which no new information was received in the reporting period

In addition to the above, there are outstanding commitments awaiting final data for completion. These include the below:

Growth and development: Awaiting results of the Mulitmodal Treatment of Attention Deficit Hyperactivity Disorder study. Marketing authorisation holders will evaluate the final report and update the core Risk Management Plan and core Summary of Product Characteristics/Product Information Leaflet as appropriate.

Long-term effects: The marketing authorisation holders have complied with the conclusions of the Article 31 referral to undertake a feasibility study on the ability to undertake long-term safety studies. The marketing authorisation holders have considered unfeasible to undertake further long-term studies in order to address the safety issues identified through the Article 31 referral and have committed to monitor external research efforts. This has been acknowledged by the Medicines and Healthcare Products Regulatory Agency who requested marketing authorisation holders to monitor the European long-term observational study of methylphenidate in children and adolescents, Attention Deficit Hyperactivity Drugs Use Chronic Effects, funded through the European Commission 7th framework.

Other Health Authority Requests

France: ANSM Requests: Patient Information Sheet (France) and Request for in vitro study to investigate affinity of methylphenidate for 5HT-2B receptors

The French Health Authority posted a Patient Information Sheet communication on its website concerning methylphenidate-containing medicines (including CONCERTA®) on 17 July 2013. The Patient Information Sheet was written together with the marketing authorisation holders of methylphenidate-containing medicines in France (Janssen, Novartis and Shire) and posted on the Agency website: http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Donnees-d-utilisation-et-mesures-visant-a-securiser-l-emploi-du-methylphenidate-en-France-publication-par-l-ANSM-d-un-rapport-d-analyse-et-d-une-brochure-d-information-a-destination-des-patients-et-de-leur-entourage-Point-d-information.

The Patient Information Sheet is not specific to CONCERTA® and concerns all methylphenidate-containing medicines in France. The Patient Information Sheet titled "You and the treatment of attention deficit disorder / hyperactivity disorder with methylphenidate" highlights the risks associated with methylphenidate, the monitoring requirements and rules of use.

On 20 March 2013, the Agency also requested methylphenidate marketing authorisation holders in France to conduct experimental studies concerning methylphenidate and its metabolite ritalinic acid on 5HT2B receptors. Study findings were submitted end of June 2013. The effects of d,l-methylphenidate and ritalinic acid were investigated in the 5-HT2B filtration receptor binding and the FDSS calcium flux assays. d,l-methylphenidate was active in the binding assay at an average IC_{50} of 9.7 µM and showed a weak agonist activity in the calcium flux assay with an average EC_{50} of 24.8 µM. Ritalinic acid was found negative in both assays. The study is currently under assessment by the French Health Authority.

Conclusions

After the period of this update, the following previously unrecognised ADRs with OROS methylphenidate hydrochloride were identified:

- Priapism
- Increased Libido

Evaluation of these ADRs is ongoing.

During the period of this update, no new efficacy information with OROS methylphenidate hydrochloride has been identified. Consequently, there has been no change to the efficacy section of the prescribing information or patient information (See Section 19, Conclusions and Actions).

OROS methylphenidate hydrochloride continues to have a favourable benefit-risk profile for the treatment of patients with Attention Deficit Hyperactivity Disorder. The Company will continue to monitor suspect adverse reactions in association with the use of OROS methylphenidate hydrochloride.

Continuous Company safety monitoring will ensure that updated safety information is available.

TABLE OF CONTENTS

APPROVER CREDENTIALS **2**

EXECUTIVE SUMMARY **3**

TABLE OF CONTENTS **8**

LIST OF IN-TEXT TABLES **10**

ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS **12**

1. INTRODUCTION **14**

2. WORLDWIDE MARKETING AUTHORISATION STATUS **14**

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS **15**

4. CHANGES TO REFERENCE SAFETY INFORMATION **18**

5. ESTIMATED EXPOSURE AND USE PATTERNS **18**
5.1. Cumulative Subject Exposure in Clinical Trials 18
5.2. Cumulative and Interval Patient Exposure From Marketing Experience 21

6. DATA IN SUMMARY TABULATIONS **25**
6.1. Reference Information 28
6.2. Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials 28
6.3. Cumulative and Interval Summary Tabulations From Post-marketing Data Sources 28

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL **29**
7.1. Completed Clinical Trials 29
7.1.1. JNS001-JPN-A01 29
7.1.2. JNS001-JPN-A02 34
7.2. Ongoing Clinical Trials 38
7.3. Long-Term Follow-up 38
7.4. Other Therapeutic Use of Medicinal Product 38
7.5. New Safety Data Related to Fixed Combination Therapies 38

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES **38**

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES **40**
9.1. Other Clinical Trials 40
9.2. Medication Errors 40

10. NON-CLINICAL DATA **40**

11. LITERATURE **40**

12. OTHER PERIODIC REPORTS **41**

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS **41**

14. LATE-BREAKING INFORMATION **41**

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED **42**

16. SIGNAL AND RISK EVALUATION **43**
16.1. Summary of Safety Concerns 43
16.2. Signal Evaluation 43
16.2.1. Other Important Safety Topics 48

16.2.1.1. Cases With Fatal Outcome 48
16.2.1.2. Neoplasms, Benign, Malignant and Unspecified (Including Cysts and Polyps) 52
16.2.1.3. Nervous System Disorders: Strokes and Cerebrovascular Events 54
16.2.1.4. Psychiatric Disorders: Depression and Suicide/Self Injury 58
16.2.2. Efficacy-Related Information 72
16.2.3. Drug Interactions 76
16.2.4. Experience With Overdose, Deliberate or Accidental, and Its Treatment 81
16.2.5. Drug Abuse/ Misuse or Medication Error/Maladministration 86
16.2.5.1. Drug Abuse/Misuse (Including Drug Diversion) 86
16.2.5.2. Medication Error/Maladministration 91
16.3. Evaluation of Risks and New Information 101
16.3.1. New Information on Important Identified Risks 101
16.3.2. New Information on Important Potential Risks 101
16.3.3. New Information on Other Identified Risks not Categorised as Important 101
16.3.4. New Information on Other Potential Risks not Categorised as Important 101
16.3.5. Update on Important Missing Information 101
16.3.5.1. Positive and Negative Experience During Pregnancy or Lactation 101
16.3.5.2. Experience in Special Patient Groups 103
16.3.5.2.1. Renal Dysfunction 103
16.3.5.2.2. Hepatic Dysfunction 105
16.3.5.2.3. Use in Elderly 106
16.3.5.2.4. Use in Children 106
16.3.5.3. Effects of Long-Term Treatment 115
16.3.6. Summary of Other Risks 118
16.3.6.1. Cardiac Disorders: Ischaemic Cardiac Events 118
16.3.7. Psychiatric Disorders 122
16.3.7.1. Psychosis and Other Psychiatric Disorders 122
16.3.7.2. Tic and Tourette's Syndrome 129
16.3.8. Reproductive and Breast Disorders 132
16.3.9. Skin and Subcutaneous Disorders 137
16.4. Characterisation of Risks 139
16.5. Effectiveness of Risk Minimisation 168

17. BENEFIT EVALUATION 168
17.1. Important Baseline Efficacy/Effectiveness Information 168
17.2. Newly Identified Information on Efficacy/Effectiveness 177
17.3. Characterisation of Benefits 178

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS 179
18.1. Benefit-Risk Context – Medical Need and Important Alternatives 179
18.2. Benefit-Risk Analysis Evaluation 183

19. CONCLUSIONS AND ACTIONS 189

LIST OF IN-TEXT TABLES

Table 1: Database Overview: Completed Clinical Trials of OROS MPH 19
Table 2: Estimated Cumulative Subject Exposure, by Investigational Drug/Product, From Completed Clinical Trials 20
Table 3: Cumulative Subject Exposure to Investigational Drug/Product From Completed Clinical Trials by Age and Sex* 20
Table 4: Cumulative Subject Exposure to OROS MPH From Completed Clinical Trials by Age and Sex* 20
Table 5: Cumulative Subject Exposure to Investigational Drug/Product From Completed Clinical Trials by Race* 21
Table 6: Cumulative Subject Exposure to OROS MPH From Completed Clinical Trials by Race* 21
Table 7: Exposure to OROS MPH (01 October 2012 to 31 October 2013) 22
Table 8: Cumulative Exposure to OROS MPH (Launch to 31 October 2013) 23
Table 9: Postmarketing (Nonstudy) Exposure for OROS MPH by Age Group in Europe (01 July 2010 to 30 June 2013) 24
Table 10: Postmarketing (Nonstudy) Exposure for OROS MPH by Age Group Outside Europe (01 July 2010 to 30 June 2013) 24
Table 11: Postmarketing (Nonstudy) Exposure for OROS MPH by Gender (01 July 2010 to 30 June 2013) 25
Table 12: Summary of OROS MPH Cases and Events Received During the Reporting Period 26
Table 13: Medically Confirmed OROS MPH Cases and Events by Source, Seriousness, and Listedness 27
Table 14: Medically Unconfirmed OROS MPH Cases and Events by Source, Seriousness, and Listedness 27
Table 15: OROS MPH Non-interventional Study Ongoing Within the Reporting Period 39
Table 16: Interim Count of Selected PTs by Age and Seriousness in OROS MPH Cases Reporting Fatal Outcomes 50
Table 17: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Neoplasms, Benign, Malignant and Unspecified (Including Cysts and Polyps) 52
Table 18: Interim and Cumulative Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Stroke and Cerebrovascular Events 56
Table 19: Characteristics for OROS MPH in Selected Cases Reporting Stroke and Cerebrovascular Events 57
Table 20: Disposition of OROS MPH Cases Involving Depression and/or Suicide/Self-Injury 60
Table 21: Interim Count of Selected PTs by Seriousness in Cases With OROS MPH: Depression and Suicide/Self Injury 61
Table 22: Characteristics for OROS MPH Cases Reporting Depression and/or Suicide/Self-Injury in Patients <18-Years-old 62
Table 23: Characteristics for OROS MPH Cases Reporting Depression and/or Suicide/Self-Injury in Patients ≥18-Years-old 63
Table 24: Selected Serious OROS MPH Cases Reporting Depression and Suicide/Self injury 66
Table 25: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Lack of Efficacy 74
Table 26: OROS MPH Select Cases Reporting Drug Interaction 77
Table 27: Interim Count of Selected PTs by Seriousness in Cases With OROS MPH: Overdose, Deliberate or Accidental 82
Table 28: Interim Count of Selected PTs by Seriousness in Cases With OROS MPH: Drug Abuse/Misuse 88
Table 29: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Medication Error and Maladministration 94
Table 30: Characteristics for OROS MPH in Selected Cases Reporting Medication Error in Patients <18-years-old 95
Table 31: Characteristics for OROS MPH in Selected Cases Reporting Medication Error in Patients ≥18-years-old 96
Table 32: Characteristics for OROS MPH in Selected Cases Reporting Medication Error in Patients With No Reported Age/Age Category 97

Table 33 PTs Reported in OROS MPH Paediatric Patients <6 Years of Age and/or Age Category of Neonate and Infant 108
Table 34 PTs Reported in OROS MPH Paediatric Patients 6 to 17 Years of Age 109
Table 35 PTs Reported in OROS MPH Patients With Age Category of Infant, Child, and Adolescent 114
Table 36: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Ischaemic Cardiac Events 119
Table 37: Counts of Select PTs by Age and Seriousness in Cases With OROS MPH: Psychosis and Other Psychiatric Disorders (n=82) 123
Table 38: Characteristics for OROS MPH Cases Reporting Psychosis and Other Psychiatric Disorders in Patients 6 to 17-years-old or Age Category Neonate, Infant, Child or Adolescent (n=24) 124
Table 39: Characteristics for OROS MPH Cases Reporting Psychosis and Other Psychiatric Disorders in Patients 18 to 65 years-old (n=7) 125
Table 40: Characteristics for OROS MPH Cases Reporting Psychosis and Other Psychiatric Disorders in Patients With No Reported Age/Age Category (n=14) 125
Table 41: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Tics and Tourette's Disorders 130
Table 42: Characteristics for OROS MPH Cases Reporting Tics and Tourette's Disorder/Dystonia in Patients <18-years-old 131
Table 43: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Reproductive System and Breast Disorders 133
Table 44: Characteristics for OROS MPH Cases Reporting Reproductive System and Breast Disorders in Patients <18-years-old 134
Table 45: Characteristics for OROS MPH Cases Reporting Reproductive System and Breast Disorders in Patients ≥18-years-old 134
Table 46: Selected OROS MPH Cases Reporting Reproductive and Breast Disorders 135
Table 47: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Skin and Subcutaneous Tissue Disorders 138
Table 48: Important Identified Risk: Hypertension 140
Table 49: Important Identified Risk: Tachycardia 144
Table 50: Important Identified Risk: Raynaud's phenomenon 148
Table 51: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance) 150
Table 52: Important Identified Risk: Psychosis/Mania 153
Table 53: Important Identified Risk: Anorexia 156
Table 54: Important Identified Risk: Aggression 158
Table 55: Important Identified Risk: Depression 161
Table 56: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias 165

ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

Acronyms/Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ADD	Attention Deficit Disorder
ADDUCE	Attention Deficit Hyperactivity Drugs Use Chronic Effects
ADR	Adverse Drug Reaction
AE	Adverse Event
AER#	Adverse Event Report Number
AERS	Adverse Events Reporting System
AIM-A	ADHD Impact Mobile-Adult
AISRS	Adult ADHD Investigator Rating Scale
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de santé (French Health Authority)
CAADID	Conners' Adult ADHD Diagnostic Interview for DSM-IV
CAARS	Conners' Adult ADHD Rating Scale
CAARS-O:SV	Conners' Adult ADHD Rating Scale-Observer: Screening Version
CAARS-S:SV	Conners' Adult ADHD Rating Scale-Self-report: Screening Version
CCDS	Company Core Data Sheet
CGI-C	Clinical Global Impression-Global Change
CGI-S	Clinical Global Impression-Severity of Illness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	Computer Tomography Angiography
DB	Double Blind
DIBD	Developmental International Birth Date
DSM-IV-TR	Diagnostic And Statistical Manual of Mental Disorders 4th Edition Text Revision
DUS	Drug Utilisation Study
EC	European Commission
ECG	Electrocardiogram
EU	European Union
EUROCAT	Epidemiological Surveillance of Congenital Anomalies
FAERS	The FDA Adverse Event Reporting System
FAR	Final Assessment Report
FDA	Food and Drug Administration (United States)
FNH	Focal Nodular Hyperplasia
GMS	Global Medical Safety
GVP	Guideline on Good Pharmacovigilance Practices
hCG	Human Chorionic Gonadotropin
HCL	Hydrochloride
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IIS	Investigator Initiated Study
I/O	Inattention/Over activity
LOE	Lack of Effect
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction

MPH	Methylphenidate hydrochloride
MRI	Magnetic Resonance Imaging
MTA	Multimodal Treatment of Attention Deficit Hyperactivity Disorder
NCS-R	National Comorbidity Survey Replication
PBRER	Periodic Benefit Risk Evaluation Report
PIS	Patient Information Sheet
PPAA	α-Phenyl-Piperidine-Acetic Acid
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
Q-LES-Q-SF	Quality of Life and Enjoyment and Satisfaction Questionnaire
QoL	Quality of Life
RCVS	Reversible Cerebral Vasoconstriction Syndrome
RMP	Risk Management Plan
RSI	Reference Safety Information
SAE	Serious Adverse Event
SDS	Sheehan Disability Scale
SJS	Stevens-Johnson Syndrome
SKAMP	Swanson, Kotkin, Agler, M-Flynn and Pelham Combined Attention Scale
SMQ	Standardised MedDRA Query
SOC	System Organ Class (MedDRA)
TnT	Troponin T
US	United States
WBC	White Blood Count
WHO	World Health Organisation

Definitions of Terms

DIBD	The date of first approval (or authorisation) to conduct an interventional clinical trial in any country
IBD	The date of first marketing authorisation for a medicinal product granted to the marketing authorisation holder in any country
Follow-up case	A case presented in a previous PBRER/PSUR for which additional information was received in the period covered by the current PBRER/PSUR
Pre-PSUR case check case	Cases which met PBRER/PSUR reporting criteria received prior to the start date of the PBRER/PSUR, but not entered into GMS safety database until the current PBRER/PSUR reporting period
Latency	Unless otherwise defined, latency is the time from initiation of therapy to onset of adverse event
Negative dechallenge	Continued presence of an adverse event after withdrawal of a drug
Negative rechallenge	Signs and symptoms similar to those observed when the drug was previously used do not reappear when the drug is reintroduced
Positive dechallenge	Partial or complete disappearance of an adverse event after withdrawal of a drug
Positive rechallenge	Reoccurrence of similar signs or symptoms upon reintroduction of a drug
Source	Classification of reporter or case (eg, health care professional, consumer, literature, study)

1. INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER)/ Periodic Safety Update Report (PSUR) for OROS® methylphenidate hydrochloride (HCl), marketed as CONCERTA® summarises the safety data obtained by the Company from worldwide sources for the reporting period of 11 October 2012 to 31 October 2013. The content and format of this report follows International Conference on Harmonisation (ICH) E2C guidelines on the PBRER and Module VII of the Guideline on Good Pharmacovigilance Practices (GVP) on the PSUR. The Company refers to this report as the PBRER/PSUR. This is the first PBRER/PSUR covering OROS methylphenidate HCl.[1] The brand names of included medicinal products can be found in Appendix 1. The first approval of OROS methylphenidate HCl was in the United States (US) on 01 August 2000.

The registered formulation of OROS methylphenidate HCl is a prolonged-release tablet, and it is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Information regarding pharmacodynamic and pharmacokinetic properties is contained in the appended Company Core Data Sheet (CCDS).

2. WORLDWIDE MARKETING AUTHORISATION STATUS

The international birth date (IBD) is 01 August 2000 based on first approval in the US.

The PBRER/PSUR data-lock point has been designated as 31 October to align with the European Union Reference Date.

The worldwide marketing authorisation status is provided in Appendix 1. Brand names, approval dates and launch dates are included in this appendix. OROS methylphenidate HCl was newly registered in Botswana (all strengths), and Vietnam (all strengths). Additional new registrations were also obtained in the United Kingdom (under the tradename Afyna prolonged-release tablets, for all strengths) and the Netherlands (all strengths). OROS methylphenidate HCl was newly launched in Botswana (all strengths) and Egypt (18 mg). There were no other launches or registrations for OROS methylphenidate HCl during the current reporting period.

Currently, OROS methylphenidate HCl is registered in 89 countries around the world.

[1] The content and format of previous 13 reports followed the ICH E2C guidelines and European Commission Volume 9A guidelines.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

European Union:

On 23 July 2007, the Committee for Medicinal Products for Human Use (CHMP) initiated an Article 31 referral procedure for all marketing authorisation holders (MAHs) of methylphenidate-containing products in the European Union (EU).[2] This was due to concerns about cardiovascular adverse events (AEs) including sudden death; cerebrovascular disorders; and psychiatric disorders. Following discussions between the CHMP and MAHs, the Rapporteur's (Medicines and Healthcare Products Regulatory Agency [MHRA]) Final Assessment Report (FAR) was issued on 03 December 2008. A final opinion was issued on 22 January 2009. The CHMP did not restrict use of methylphenidate-containing products, but required the addition of pre-treatment screening and ongoing monitoring instructions to the prescribing information. A number of post-referral commitments for MAHs of methylphenidate containing products were also adopted by the CHMP. The CHMP opinion was ratified by the European Commission (EC) on 27 May 2009.

The following status update for the EU Article 31 referral commitments provides a summary of the outstanding actions that have been taken or were in progress during the current reporting period by the Company (and MAHs) to fulfil the Conditions of the Marketing Authorisations as adopted by the CHMP (Annex IV of EC decision; Appendix 2), hereafter referred to as 'conditions':

Sexual Maturation

As part of the EU Article 31 referral conditions, the MAHs were requested to make available the final study report of an Investigator Initiated Study (IIS) using Tanner staging examinations to evaluate effects of methylphenidate on sexual maturation. A copy of the manuscript from the IIS study was submitted to the MHRA on 12 September 2012 for information confirming the study findings that long term treatment with OROS methylphenidate does not have a detrimental effect on sexual maturation in adolescents with ADHD.

As the manuscript has not yet been accepted for publication, the MAHs consider the submission of the manuscript on 12 September 2012 as fulfilment of this condition. Should the manuscript be published in the future, then the Company will forward the report to the MHRA for review.

[2] MAHs" refers to the following Marketing Authorisation holders of methylphenidate containing products: Janssen, Novartis, Shire, Medice, and Laboratorios Rubio

Drug utilisation

As part of the EU Article 31 referral conditions, the MAHs were requested to submit annual drug utilisation data for 5 consecutive years to allow an evaluation of changes in usage over time. The Company (with other MAHs) provides on an annual basis all available retrospective drug utilisation data using health related electronic databases in all EU Member States (and additionally Switzerland) where methylphenidate is used and to the extent such databases are available. An evaluation of methylphenidate usage in 2012 will be included in the PSUR workshare submission in the EU (UK/H/PSUR/0068/005), to be submitted in December 2013 This drug utilisation study (DUS) represents the fifth and final DUS to address the Article 31 referral commitment for a drug utilisation study, which only requested retrospective data on an annual review basis for 5 years.

Educational tools

As part of the EU Article 31 referral conditions, the MAHs were requested to produce fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklists) containing all of the important information from the Clinical Particulars section of the European core SmPC for assessment. The MHRA requested further changes in its Risk Management Plan (RMP) Final Assessment Report (FAR) of September 2010. The MAHs addressed the issues raised by the MHRA and other Concerned Member States within the submission package to support UK/H/PSUR/0068/002, submitted 09 December 2010. In MHRA's RMP FAR of 26 September 2012, the MHRA confirmed the educational tools could progress to the 'national phase' and that the MAHs should proceed with obtaining national agreement of texts to obtain endorsement and allow the implementation of the tools on a per country basis.

At time of writing, approval of the educational tools has been received in the following Member States: Ireland (19 February 2013), Malta (10 October 2013), Norway (21 November 2013), Romania (24 November 2013), Spain (22 November 2013) and UK (19 September 2013). The educational tools have been submitted in the following Member States: Belgium, Bulgaria, Estonia, Greece, Iceland Italy, Lithuania, the Netherlands, Poland and Slovakia. . Submission to national Health Authorities will continue into 2014.

MHRA Request for MAHs to Further Investigate Signals for Spina Bifida/Neural Tube Defects from the World Health Organisation (WHO) Collaborating Centre for the European Surveillance of Congenital Anomalies (EUROCAT)

In the 26 September 2012 WS PSUR FAR, the MHRA requested the MAHs to address the following point in the next PSUR:

"The MAHs are requested to obtain and evaluate data to further investigate the signal for spina bifida/neural tube defects from the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT)."

In September 2012 a request was made to EUROCAT for information on cases of spina bifida/neural tube defects associated with the use of methylphenidate products in order to

identify trends or potential clusters related with the methylphenidate exposure. The following information together with the listed caveats was provided by EUROCAT on 22 October 2012:

"There are 5 cases with maternal exposure to methylphenidate (N06BA04) in the EUROCAT database, for the years 1995-2010.

Please note the following important caveats:

- At present, the 5 cases of methylphenidate exposure have not been confirmed by the contributing registries.
- Not all medication exposures are recorded by EUROCAT registries.
- This should not be interpreted as the prevalence of exposed cases of congenital anomaly in the European population. It is only a guide as to whether a study using the EUROCAT database to identify any specific malformation associated with exposure is feasible."

Further details regarding the 5 cases was requested (the type of neural tube defect experienced, the methylphenidate product (if known), concomitant medication, etc.). EUROCAT confirmed it was presently reviewing its internal medication data request procedures and could not provide additional information on the 5 cases until 2013. Janssen submitted a medication enquiry to EUROCAT in October 2013 and currently awaits a reply.

Outstanding commitments for which no new information was received in the reporting period

In addition to the above, there are outstanding commitments awaiting final data for completion. These include the below:

Growth and development: Awaiting results of the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study. MAHs will evaluate the final report and update the core RMP and core SmPC/PIL as appropriate.

Long-term effects: The MAHs have complied with the conclusions of the Article 31 referral to undertake a feasibility study on the ability to undertake long-term safety studies. The MAHs have considered unfeasible to undertake further long-term studies in order to address the safety issues identified through the Article 31 referral and have committed to monitor external research efforts. This has been acknowledged by the MHRA who requested MAHs to monitor the European long-term observational study of MPH in children and adolescents, Attention Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) funded through the EC 7th framework.

Other Health Authority Requests

France: ANSM Requests: Patient Information Sheet (France) and Request for *in vitro* study to investigate affinity of methylphenidate for 5HT-2B receptors

The French Health Authority (ANSM) posted a Patient Information Sheet (PIS) communication on its website concerning methylphenidate-containing medicines (including CONCERTA®) on 17 July 2013. The PIS was written together with the MAHs of methylphenidate-containing medicines in France (Janssen, Novartis and Shire) and posted on the Agency website: http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Donnees-d-utilisation-et-mesures-visant-a-securiser-l-emploi-du-methylphenidate-en-France-publication-par-l-ANSM-d-un-rapport-d-analyse-et-d-une-brochure-d-information-a-destination-des-patients-et-de-leur-entourage-Point-d-information.

The PIS is not specific to OROS methylphenidate HCl and concerns all methylphenidate-containing medicines in France. The PIS titled "You and the treatment of attention deficit disorder / hyperactivity disorder with methylphenidate" highlights the risks associated with methylphenidate, the monitoring requirements and rules of use.

On 20 March 013, the Agency also requested MPH MAHs in France to conduct experimental studies concerning MPH and its metabolite ritalinic acid (PPA) on 5HT2B receptors. Study findings were submitted end June 2013. The effects of *d,l*-methylphenidate and ritalinic acid were investigated in the 5-HT2B filtration receptor binding and the FDSS calcium flux assays. *d,l*-methylphenidate was active in the binding assay at an average IC_{50} of 9.7 µM and showed a weak agonist activity in the calcium flux assay with an average EC_{50} of 24.8 µM. Ritalinic acid was found negative in both assays. The study is currently under assessment by the ANSM.

4. CHANGES TO REFERENCE SAFETY INFORMATION

There were no changes to the CCDS during the reporting period.

The CCDS in effect throughout the reporting period for OROS methylphenidate HCl is dated May 2012 and is attached as Appendix 2.

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

During the period of this review, approximately 205 study subjects were exposed to OROS methylphenidate HCl in a Company-sponsored interventional clinical study (JNS001-JPN-A02, discussed in Section 7.1.2.).

The clinical development for OROS methylphenidate HCl was initiated 20 years ago. Since that time, OROS methylphenidate HCl has been studied in numerous Company-sponsored trials. Due to the maturity of the product, in terms of its clinical development, a reliable, precise estimate of subjects exposed in all Company-sponsored clinical trials with OROS methylphenidate HCl is not available. In this respect, however, the subject exposures in 7 placebo-controlled, or active-controlled, double-blind clinical trials, and 20 open-label clinical trials of OROS methylphenidate HCl are described in Section “Adverse Reactions” of the CCDS.

This section enumerates and describes subjects exposed to study medication in the clinical programme that supported the baseline efficacy/effectiveness and safety information as

represented in the CCDS. In addition, subjects from two post-approval trials in paediatrics and one in adults are included. An overview of all of these studies is presented in Table 1.

Table 1: Database Overview: Completed Clinical Trials of OROS MPH

Study ID	Study Population	Age Group	Design	Notes
02159	Adult	Adult (>=18)	Double-Blind	Some subjects went into 12304 OL
3002/ 3004	Adult	Adult (>=18)	Double-Blind + Open Label	Some subjects went into Adult 3004 OL
3013	Adult	Adult (>=18)	Double-Blind	
3014	Adult (post-approval)	Adult (>=18)	Double-Blind	349 safety subjects
CONCAN4	Adult	Adult (>=18)	Open Label	
C99018	Adult	Adult (>=18)	Open Label	
12304	Adult	Adult (>=18)	Open Label	Some subjects coming from Adult 02159 DB
C97025	Pediatric	Children (6-12)	Double-Blind	Crossover
C98003	Pediatric	Children (6-12)	Double-Blind	Crossover
C98005	Pediatric	Children (6-12)	Double-Blind	
CONCAN1	Pediatric	Children (6-12)	Open Label	
CONCAN2	Pediatric	Children (6-12)	Open Label	
C98007	Pediatric	Children (6-12)	Open Label	
C98012	Pediatric	Children (6-12)	Open Label	
12101	Pediatric	Children (6-12)	Open Label	
4069	Pediatric (post-approval)	Children (6-12)	Open Label	71 safety subjects
4080	Pediatric (post-approval)	Children (6-12)	Open Label	68 safety subjects
C2000045	Pediatric	Children (6-12), Adolescents (13 to 17)	Open Label	
C99018	Pediatric	Children (6-12), Adolescents (13 to 17)	Open Label	
01146	Pediatric	Adolescents (13 to 17)	Open Label Titration + Double-Blind + Open label	

Key: MPH=Methylphenidate hydrochloride

In these studies, 5,271 subjects with ADHD were enrolled in the OROS methylphenidate HCl clinical programme, of which approximately 4,428 subjects received OROS methylphenidate HCl (see Table 2). Table 3 and Table 5 show cumulative subject exposure by age and sex, first to Investigational Drug/Product and then to OROS methylphenidate HCl, respectively. Table 5 and Table 6 show cumulative subject exposure by race, first, to Investigational Drug/Product and then to OROS methylphenidate HCl, respectively. A simple summation of numbers to correlate subject numbers between these tables is not possible because some subjects participated in the comparative studies and then participated in extension studies, or in crossover studies. Subject exposures were counted only once per subject.

While a clinical study report regarding the completed clinical trial has been issued, JNS001 JPN A01 (discussed in Section 7.1.1. JNS001 JPN A01), with the last observation date of last subject in April 2012, the database has not become available. Therefore, the cumulative exposure tables, below, do not include the 284 subjects (143 for OROS methylphenidate HCl, 141 for placebo) who received at least 1 dose of the study drug (safety analysis set). These data will be incorporated in subsequent editions of this document.

Table 2: Estimated Cumulative Subject Exposure, by Investigational Drug/Product, From Completed Clinical Trials

	Number of Subjects			
Treatment	Children	Adolescents	Adults	Total
Placebo	367	90	484	941
Comparator[a]	783	0	0	783
OROS Methylphenidate HCl	2,383	502	1,543	4,428

Key: HCl= hydrochloride
a: Comparators include Atomoxetine hydrochloride, IR MPH

Table 3: Cumulative Subject Exposure to Investigational Drug/Product From Completed Clinical Trials by Age and Sex*

	Number of Subjects		
Age Range (years)	Male	Female	Total
< 6	18	2	20
6 to 12	2,178	649	2,827
13 to 17	422	97	519
18 to 35	542	375	917
36 to 49	358	363	721
50 to 66	126	138	264
Missing	1	1	2

*Data from completed trials as of 31 October 2013
Note: One subject from study 12-101 had missing value for sex

Table 4: Cumulative Subject Exposure to OROS MPH From Completed Clinical Trials by Age and Sex*

	Number of Subjects		
Age Range (years)	Male	Female	Total
< 6	13	2	15
6 to 12	1822	526	2348
13 to 17	411	97	508
18 to 35	439	302	741
36 to 49	292	292	584
50 to 66	107	122	229
Missing	1	1	2

*Data from completed trials as of 31 October 2013
Note: One subject from study 12-101 had missing value for sex

Table 5: Cumulative Subject Exposure to Investigational Drug/Product From Completed Clinical Trials by Race*

Race Group	Number of Subjects			
	Children	Adolescents	Adults	Total
Asian	15	6	29	50
Black/African American	311	45	91	447
White Or Caucasian	2,239	403	1,719	4,361
Hispanic	132	16	0	148
American Indian/Alaskan Native	4	0	1	5
Native Hawaiian/Other Pacific Islander	1	0	2	3
Other	88	14	45	147
Unknown	91	18	1	110
Total	2,881	502	1,888	5,271

*Data from completed trials as of 31 October 2013.

Table 6: Cumulative Subject Exposure to OROS MPH From Completed Clinical Trials by Race*

Race Group	Number of Subjects			
	Children	Adolescents	Adults	Total
Asian	13	6	22	41
Black/African American	251	45	68	364
White Or Caucasian	1845	403	1417	3665
Hispanic	102	16	0	118
American Indian/Alaskan Native	3	0	0	3
Native Hawaiian/Other Pacific Islander	1	0	1	2
Other	78	14	34	126
Unknown	90	18	1	109
Total	2383	502	1543	4428

*Data from completed trials as of 31 October 2013.

5.2. Cumulative and Interval Patient Exposure From Marketing Experience

Post-Marketing Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient.

Patient Exposure (Person-Time)

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. OROS methylphenidate HCl should be taken once per day. The average month is [redacted] days. Therefore, [redacted] person-month of exposure. The exposure for the current period is presented in Table 7.

Table 7: Exposure to OROS MPH (01 October 2012 to 31 October 2013)

Region	Country	Tablets	Person-Months	Person-Years
European Union	Austria	[redacted]		
	Belgium			
	Bulgaria			
	Cyprus			
	Czechia			
	Denmark			
	Estonia			
	Finland			
	France			
	Germany			
	Greece			
	Ireland			
	Latvia			
	Lithuania			
	Malta			
	Netherlands			
	Poland			
	Portugal			
	Roumenia			
	Slovakia			
	Slovenia			
	Spain			
	Sweden			
	U.K.			
Subtotal				
North America				
Rest of World [a]				
Switzerland	Switzerland			
Total				

Key: MPH=Methylphenidate hydrochloride

a: Rest of World does not include Switzerland in this table since it has been reported separately.

Based on the 279,790,823 tablets of OROS methylphenidate HCl distributed (from 01 October 2012 to 31 October 2013), the estimated exposure is 9,203,645 person-months or 766,973 person-years. The exposure in the current period is approximately 8% lower than the previous 13-month period (01 September 2011 to 30 September 2012).

Cumulative Exposure Estimate

Table 8: Cumulative Exposure to OROS MPH (Launch to 31 October 2013)

Region	Country	Tablets	Person-Months	Person-Years
European Union				
	Austria	[redacted]		
	Belgium			
	Bulgaria			
	Cyprus			
	Czechia			
	Denmark			
	Estonia			
	Finland			
	France			
	Germany			
	Greece			
	Ireland			
	Latvia			
	Lithuania			
	Malta			
	Netherlands			
	Poland			
	Portugal			
	Roumenia			
	Slovakia			
	Slovenia			
	Spain			
	Sweden			
	U.K.			
Subtotal				
North America				
Rest of World [a]				
Switzerland	Switzerland			
Total				

Key: MPH=Methylphenidate hydrochloride

a: Rest of World does not include Switzerland in this table since it has been reported separately.

Based on the [redacted] tablets of OROS methylphenidate HCl distributed by the company (from launch to 31 October 2013), the estimated exposure is [redacted] person-months or [redacted] person-years.

Additional Stratifications for OROS Methylphenidate HCL:

Additional stratifications are provided using IMS data where possible and appropriate. Market research sources for non-study exposure data are unavailable for breakdowns such as: usage in pregnant or breast feeding women, usage in hepatic impairment population, usage in renal impairment population.

Exposure by age and gender presented as a percentage of Prescription sales:

Prescription sales stratified by age and gender available from IMS MIDAS™ and are presented below (as a percentage of total prescriptions). All information presented for stratification data is from IMS MIDAS™ syndicated audit.

Further splits such as gender within age group are not provided since it is not appropriate to stratify to this level of detail based on prescription information available from IMS for these subcategories. Prescription units are reported as absolute values.

Table 9: Postmarketing (Nonstudy) Exposure for OROS MPH by Age Group in Europe (01 July 2010 to 30 June 2013)

Age groups (years) [a]	EU [b] [redacted]
[redacted]	0.14%
6-10	20.99%
11-15	49.92%
16-20	19.03%
21-65	9.63%
>65	0.05%
Age not specified	0.24%

Key: EU=Europe, MPH=Methylphenidate hydrochloride
a: Regional Rx data by age are only available for the last 3 years ending 30 June 2013.
b: Data stratified by age are only available in France, Germany, Spain and United Kingdom.
c: Rx = Prescriptions, includes retail channels.

Table 10: Postmarketing (Nonstudy) Exposure for OROS MPH by Age Group Outside Europe (01 July 2010 to 30 June 2013)

Age groups (years) [a]	**Non-EU [b] ([redacted])**
<6	0.97%
6-10	32.72%
11-15	36.95%
16-20	13.66%
21-65	12.96%
>65	0.43%
Age Unspecified	2.31%

Key: EU=Europe, MPH=methylphenidate
a: Regional Rx data by age are only available for the last 3 years ending 30 June 2013.
b: Data stratified by age are only available in Canada, Japan and United States.
c: Rx = Prescriptions, includes retail channels.

Table 11: Postmarketing (Nonstudy) Exposure for OROS MPH by Gender (01 July 2010 to 30 June 2013)

	Females [a]	Males [a]	Patient Gender Unidentified [a]
France	29.00%	69.09%	1.91%
Germany	20.70%	79.27%	0.03%
Spain	22.33%	76.87%	0.80%
United Kingdom	18.54%	81.46%	0%
Canada	26.93%	71.43%	1.64%
Japan	7.77%	90.30%	1.93%
US	28.83%	68.72%	2.45%

Key: MPH=Methylphenidate hydrochloride

a: Regional Rx data by age are only available for the last 3 years ending 30 June 2013. Data are only available for France, Germany, Spain, United Kingdom, Canada, Japan and United States.

b: Rx = prescriptions, includes retail channels.

Post-authorisation use in special populations

There is no available information on post-authorisation use of OROS methylphenidate HCl in special populations.

Pattern of use of the medicinal product

There is no available information on pattern of use of OROS methylphenidate HCl which may be considered relevant for the interpretation of safety data.

6. DATA IN SUMMARY TABULATIONS

Database

The Global Medical Safety (GMS) safety database contains AE reports received from several sources:

- Cases reporting serious and nonserious AEs from spontaneous notification.
- Cases reporting serious and nonserious AEs from regulatory authorities.
- Cases reporting serious and nonserious AEs retrieved from the medical literature.
- Cases received from clinical trials, post-marketing studies, registries and solicited sources.

Cases with minimal information are included providing they fulfil minimum criteria to meet regulatory reporting requirements.

Listedness for all AEs is based upon the CCDS in effect at the time the AE was initially assessed.[3]

[3] When applicable, clinical trial cases are assessed against the Investigator's Brochure or other chosen reference safety information, depending on the type of trial.

In accordance with standard operating procedures, attempts to obtain follow-up information for AEs and special reporting situations are made to obtain complete Individual Case Safety Reports (ICSRs). For incomplete reports originating from healthcare professionals, 2 attempts are made to obtain follow-up information pertaining to serious unlisted ICSRs, and 1 attempt is made for serious listed and nonserious unlisted ICSRs. For incomplete reports originating from consumers, a minimum of 2 attempts are made to obtain authorisation for disclosure of medical information pertaining to serious ICSRs, whereas a minimum of 1 attempt is made for nonserious unlisted ICSRs. For specified events of special interest, follow-up attempts are guided by case level seriousness with a minimum of 2 follow-up attempts made for all serious ICSRs and a minimum of 1 follow-up attempt for all nonserious ICSRs. An exception to this is made for pregnancy exposure (maternal and paternal) and exposure to a Company medicinal product from breastfeeding, which requires a minimum of 2 follow-up attempts.

Follow-up information to cases in previous PBRERs/PSURs is included in the appended line listings if new versions were created during the reporting period.

The line listings are separated into 3 reports.

- Medically Confirmed Serious Unlisted, Serious Listed and Nonserious Unlisted AEs: hereafter, referred to as the "Core Report" (see Appendix 3.3).
- Medically Confirmed Nonserious Listed AEs: hereafter, referred to as the "Nonserious, Listed Report" (see Appendix 3.4).
- Medically Unconfirmed AEs: hereafter, referred to as the "Medically Unconfirmed Report" (see Appendix 3.5).

During the reporting period, the numbers of cases and AEs received for OROS methylphenidate HCl are presented in Table 12. The total number of events may exceed the total number of cases as 1 case can include more than 1 event.

Table 12: Summary of OROS MPH Cases and Events Received During the Reporting Period

	Number of Cases[a]		Number of Events[a]	
	Initial	**Follow-up**	**Initial**	**Follow-up**
Medically Confirmed	1077	87	2253	197
Medically Unconfirmed	710	26	1731	104

Key: MPH=Methylphenidate hydrochloride
a: Figures are obtained from counting cases/events on the appended line listings in Appendices 3.3, 3.4 and 3.5.

A further breakdown of this information according to source, medical confirmation, seriousness and listedness is provided in Table 13 and Table 14.

Table 13: Medically Confirmed OROS MPH Cases and Events by Source, Seriousness, and Listedness

	Cases[a]			Events[b]				
				Serious		Nonserious		
	Core	Nonserious Listed	Total Cases	Unlisted	Listed	Unlisted	Listed	Total Events[b]
Initial Spontaneous	634	274	908	262	199	575	672	1708
Initial Clinical Trial	1	0	1	0	2	7	10	19
Initial Literature	134	33	167	93	69	120	242	524
Initial Solicited	1	0	1	0	1	0	1	2
Initial Medically Confirmed Total	**770**	**307**	**1077**	**355**	**271**	**702**	**925**	**2253**
Follow-up Spontaneous	61	15	76	58	22	39	50	169
Follow-up Clinical Trial	2	0	2	1	1	0	0	2
Follow-up Literature	6	2	8	15	0	2	8	25
Follow-up Solicited	1	0	1	0	1	0	0	1
Follow-up Medically Confirmed Total	**70**	**17**	**87**	**74**	**24**	**41**	**58**	**197**

Key: MPH=Methylphenidate hydrochloride
a: Figures are obtained from counting cases/events on the appended line listings in Appendices 3.3 and 3.4.
b: Note that a case may report more than 1 event.

Table 14: Medically Unconfirmed OROS MPH Cases and Events by Source, Seriousness, and Listedness

	Cases[a]	Events[b]				
		Serious		Nonserious		
	Total Cases	Unlisted	Listed	Unlisted	Listed	Total Events[b]
Initial Spontaneous	707	122	85	626	887	1720
Initial Clinical Trial	0	0	0	0	0	0
Initial Literature	2	0	0	4	4	8
Initial Solicited	1	2	1	0	0	3
Initial Medically Unconfirmed Total	**710**	**124**	**86**	**630**	**891**	**1731**
Follow-up Spontaneous	26	7	8	36	53	104
Follow-up Clinical Trial	0	0	0	0	0	0
Follow-up Literature	0	0	0	0	0	0
Follow-up Solicited	0	0	0	0	0	0
Follow-up Medically Unconfirmed Total	**26**	**7**	**8**	**36**	**53**	**104**

Key: MPH=Methylphenidate hydrochloride
a: Figures are obtained from counting cases/events on the appended line listings in Appendix 3.5.
b: Note that a case may report more than 1 event.

Additionally, 4 medically confirmed cases which met PBRER/PSUR reporting criteria were received prior to the start date of this PBRER/PSUR, but were not entered into the GMS safety database until the current PBRER/PSUR reporting period.

These cases do not appear in the standard line listings and are not included in the tables above. A line listing of these 4 cases is attached as Appendix 7.2.

These cases were reviewed for potential medical significance. They are only discussed within the body of this report if they provide additional meaningful information in the context of an analysis of a particular safety issue and/or if they contain potentially new information.

6.1. Reference Information

All events are coded using Medical Dictionary for Regulatory Activities (MedDRA, version 16.1). Caution is advised when comparing current data with those of PBRERs/PSURs using earlier MedDRA versions/coding dictionaries.

6.2. Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials

Appendix 3.1 contains a cumulative tabulation of serious AEs (SAEs) from clinical trials, reported from the Development International Birth Date (DIBD) to the data lock date of this PBRER/PSUR. SAEs are included regardless of causality (ie, related and not related SAEs are included).

SAEs from blinded and unblinded clinical trials cases are included. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related reasons (eg, expedited reporting), if applicable. Data has not been unblinded for the specific purpose of preparing the PBRER/PSUR. SAEs are organised by MedDRA System Organ Class (SOC) for the investigational product, and comparators (active and placebo).

Protocols 12-001, CCT-TWN-MA1, CONCERTA-ATT-4099, CONCERTA-ATT-4086, and 42603-CAN-T1 are not included in the Cumulative Tabulation of SAEs; however, no SAEs have been reported for these protocols up to 31 October 2013.

Applicable legacy data was added to this tabulation.

6.3. Cumulative and Interval Summary Tabulations From Post-marketing Data Sources

Appendix 3.2 contains cumulative and interval summary tabulations of adverse reactions from the IBD to the data lock date of this PBRER/PSUR. These adverse reactions are derived from non-interventional studies and spontaneous notification, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities.

Applicable legacy data was added to this tabulation.

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

Appendix 4 contains a listing of the Company-sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk minimisation measures that were completed or ongoing during the reporting interval.

7.1. Completed Clinical Trials

Two OROS methylphenidate HCl studies that were completed during the PBRER/PSUR reporting period are presented in this section.

7.1.1. JNS001-JPN-A01

Title of Study: A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of JNS001 in Adults with Attention Deficit/Hyperactivity Disorder at Doses of 18 mg, 36 mg, 54 mg or 72 mg per day.[4] (Clinical Study Report became available during the reporting period but no patients were exposed in this interval).

Study Period: March 2011 (first subject informed consent date) to April 2012 (last observation date of last subject).

Primary Objective: The primary objective was to evaluate the efficacy of JNS001 (OROS methylphenidate HCl) titrated to daily dose of 18 to 72 mg in adults with ADHD relative to placebo, based on the change in Diagnostic And Statistical Manual of Mental Disorders 4th Edition (DSM-IV) Total ADHD Symptoms scores (18 items) of the investigator-rated Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV) from baseline to the end of the double-blind (DB) phase.

Methodology: This was a randomised, DB, multicentre, placebo-controlled, parallel group, dose-titration study. The study consisted of a 1 to 2-week screening phase (including washout), an 8-week DB phase (4-week titration period and 4-week efficacy assessment period), and a 1-week Post-study phase. Eligible subjects were randomly assigned in a ratio of 1:1 to receive OROS methylphenidate HCl or placebo once daily. Subjects were titrated from a starting dose of 18 mg per day at weekly increments of 18 mg per day to an individually-optimised dose at which the CAARS-O:SV score had improved by 30% from baseline and a Clinical Global Impression-Global Change (CGI-C) rating of 1 or 2 (very much improved/much improved) was achieved or to a maximum dose of 72 mg per day. The subjects were to remain on this dose for the remainder of the study, if possible. Safety was evaluated throughout the study and efficacy evaluations were performed at baseline and at designated time points in the DB phase. Pharmacokinetic samples were obtained at Weeks 4 and 8. The Post-study phase was held for all subjects who received study treatment.

[4] Clinical Study Report JNS001-JPN-A01. Double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of JNS001 in adults with attention-deficit/hyperactivity disorder at doses of 18 mg, 36 mg, 54 mg or 72 mg per day. Document ID No.: EDMS-ERI-64229895; Janssen Pharmaceutical K.K. (20 November 2012).

Diagnosis and Main Criteria for Inclusion: Men and women, between 18 and 64 years old, inclusive, with a diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR) criteria (Conners' Adult ADHD Diagnostic Interview for DSM-IV [CAADID] Japanese version) and DSM-IV Total ADHD Symptoms scores of CAARS-O:SV score of ≥24.

Criteria for Evaluation: Pharmacokinetic samples for concentrations of methylphenidate (MPH) and its major metabolite α-phenyl-piperidine-acetic acid (PPAA) were collected at Weeks 4 and 8 (Day 28 and 56) or at early discontinuation in the DB phase.

The primary efficacy outcome measure was the CAARS-O:SV: DSM-IV ADHD Symptom scales. Other efficacy assessments included the Conners' Adult ADHD Rating Scale-Self-report: Screening Version (CAARS-S:SV): DSM-IV ADHD Symptom scales, Clinical Global Impression-Severity of Illness (CGI-S) score, CGI-C score, and Quality of Life and Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) total score.

Safety assessment was based on reported AEs, clinical laboratory tests, vital sign and body weight measurements, electrocardiograms (ECG), evaluations of sleep, appetite, and abuse potential, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Results:

Study Population: Eligible subjects (N=284) were enrolled in the study and randomly assigned to receive OROS methylphenidate HCl or placebo. All of the 284 subjects (143 for OROS methylphenidate HCl, 141 for placebo) received at least 1 dose of the study drug (safety analysis set), of which 283 subjects (143 for OROS methylphenidate HCl, 140 for placebo) had both baseline and postbaseline efficacy data (full analysis set). Pharmacokinetic analyses were based on 142 subjects who had at least 1 plasma MPH concentration available for the evaluation of pharmacokinetics (pharmacokinetic analysis set).

Of the 284 randomised and treated subjects, 134 subjects (93.7%) in the OROS methylphenidate HCl group and 135 subjects (95.7%) in the placebo group completed the DB phase. Nine subjects (6.3%) in the OROS methylphenidate HCl group and 6 subjects (4.3%) in the placebo group discontinued study treatment in the DB phase. The most common reasons for discontinuation were adverse events (6 subjects) in the OROS methylphenidate HCl group and noncompliance with study drug (3 subjects) in the placebo group.

All of the demographic and baseline characteristics were well balanced between the 2 treatment groups. The subjects' age ranged from 18 to 59 years, with a mean age of 33.4 and 34.1 years in the OROS methylphenidate HCl and placebo groups, respectively. Overall, the age at initial ADHD diagnosis ranged from 1 to 58 years, with a mean age of 31.4 and 32.4 years in the OROS methylphenidate HCl and placebo groups, respectively. All subjects in both groups met the diagnostic criteria for ADHD according to DSM-IV-TR at present and in childhood based on CAADID.

Within 3 months prior to screening, 14.7% subjects in the OROS methylphenidate HCl group and 12.1% subjects in the placebo group received 1 or more psychotropic agents for ADHD. The most commonly used psychotropic agents for ADHD were atomoxetine hydrochloride and pemoline. More subjects in the placebo group (14.2%) than in the OROS methylphenidate HCl group (9.1%) received hypnotics during the DB phase. The frequency of use of antianxiety drugs during the DB phase was generally similar in both groups.

The mean duration of exposure to study drug (including days with missed intakes) was 54.0 days in the OROS methylphenidate HCl group and 55.1 days in the placebo group. The majority of subjects (93% or greater) in both groups received the study drug for at least 50 days.

Pharmacokinetic Results:

From 142 subjects included in the pharmacokinetic analysis set, 277 plasma MPH concentrations and 277 plasma PPAA concentrations (a total of 554 concentrations) were included in the pharmacokinetic analysis.

Individual plasma concentrations of MPH and PPAA at Week 8 (the end of the DB phase) were generally similar to those at Week 4 (the end of the titration period). This indicates that plasma concentrations of MPH and PPAA reached steady state by Week 4 and were maintained thereafter till the end of the DB phase with subject's individualised doses. Mean plasma concentrations of MPH and PPAA at Week 4 and 8 increased with dose, within a dose range of 18 to 72 mg.

Efficacy Results:

The baseline mean (SD) total ADHD Symptoms scores were similar between the treatment groups: 31.8 (5.96) in the OROS methylphenidate HCl group and 31.5 (6.44) in the placebo group. Based on the ANCOVA model, the LS mean change from baseline to the end point in the total scores was -12.5 (95% Confidence interval [CI]: -14.0 to -11.0) in the OROS methylphenidate HCl group and -7.9 [95% CI: -9.5 to -6.4] in the placebo group. The LS mean difference (SE) from placebo was -4.5 (1.10) for the OROS methylphenidate HCl group at end point (LOCF). The magnitude of improvement in the total ADHD Symptoms scores was statistically significantly larger in the OROS methylphenidate HCl group than in the placebo group ($p<0.0001$, ANCOVA). Sensitivity analyses confirmed the robustness of the results of the primary analysis. The statistical superiority of OROS methylphenidate HCl over placebo in reducing the total ADHD symptoms scores was initially observed at Week 2, and was maintained thereafter through the end of the DB phase. Primary endpoint results indicated that OROS methylphenidate HCl titrated to a daily dose of 18 to 72 mg significantly improved ADHD symptoms with onset of efficacy at 2 weeks after treatment initiation.

The results of secondary endpoints consistently supported the superior efficacy of OROS methylphenidate HCl over placebo in adult subjects with ADHD. OROS methylphenidate HCl also reduced the severity of both inattentive symptoms and hyperactivity-impulsivity symptoms, as shown by the statistically significantly greater improvement compared to placebo in the CAARS-O:SV "Inattentive symptoms" and "Hyperactive-Impulsive symptoms" subscales. The LS mean difference (SE) from placebo for OROS methylphenidate HCl in these subscale

scores was -3.1 (0.72) for "Inattentive symptoms" and -1.4 (0.51) for "Hyperactive-Impulsive symptoms" at end point (LOCF).

In addition, the subject self-reported CAARS-S:SV scale and the investigator-rated CGI-S and CGI-C scales demonstrated a significantly greater effect of OROS methylphenidate HCl relative to placebo in reducing the severity of ADHD symptoms. The LS mean difference (SE) from placebo for OROS methylphenidate HCl in CAARS-S:SV total ADHD symptoms scores and total score was -4.1 (1.11) and -6.9 (1.86), respectively, at end point (LOCF). At end point, the improvement in CGI-S and CGI-C score was statistically significantly greater in the OROS methylphenidate HCl group than in the placebo group (CGI-S, $p<0.0001$ [ANCOVA]; CGI-C, $p<0.0001$ [ANOVA]). For the CGI-S scale, the percentage of subjects assessed as "moderately ill" or worse decreased from 97.2% at baseline to 43.4% at end point in the OROS methylphenidate HCl group, and from 92.9% to 62.1% in the placebo group. For the CGI-C scale, the percentage of subjects assessed as "much improved" or "very much improved" was 48.3% in the OROS methylphenidate HCl group and 27.9% in the placebo group at end point.

These efficacy results demonstrated that daily dosing of OROS methylphenidate HCl for 8 weeks at individualised doses titrated from 18 to 72 mg is superior to placebo in the treatment of ADHD in adult patients in Japan.

Safety Results:

The incidence of adverse events in subjects in the OROS methylphenidate HCl group was higher than in the placebo group (81.8% vs 53.9%). The most commonly reported adverse events (≥5% of subjects) in the OROS methylphenidate HCl group were decreased appetite (39.9%), palpitations (18.2%), nasopharyngitis (16.8%), nausea (14.7%), thirst (14.0%), insomnia (10.5%), headache (8.4%), weight decreased (7.0%), and tachycardia (5.6%). All adverse events (except 2 serious adverse events) were mild to moderate in severity with type and frequency of adverse events generally similar for men and women.

Two subjects (1.4%) in the OROS methylphenidate HCl group experienced 1 serious adverse event each during the DB Phase. A [redacted] developed a severe psychotic disorder and [redacted] discontinued study treatment due to the serious adverse event. The causal relationship to the study drug could not be ruled out by the investigator. A [redacted] experienced severe pneumothorax spontaneous tension, which was judged by the investigator to be not related to the study drug. The [redacted] recovered from the serious adverse event during the DB Phase.

No deaths occurred in this study.

During the DB Phase, 6 subjects (4.2%) in the OROS methylphenidate HCl group permanently discontinued study treatment due to adverse events of decreased appetite (reported in 2 subjects); anxiety, insomnia, psychotic disorder, dizziness, palpitations, nausea, and thirst (reported in 1 subject each). In the placebo group 1 subject (0.7%) permanently discontinued study treatment due to adverse event of mania.

No dominant adverse events indicative of a withdrawal phenomenon during the Post-study Phase were observed.

During the DB Phase, the adverse events of special interest related to decreased appetite, weight decrease and growth (40.6% for OROS methylphenidate HCl vs. 7.1% for placebo) and adverse events related to cardiovascular disorders (21.0% for OROS methylphenidate HCl vs. 1.4% for placebo) were more common in the OROS methylphenidate HCl group than in the placebo group. The adverse events related to initiating or maintaining sleep (11.9% for OROS methylphenidate HCl vs. 10.6% for placebo) and adverse events related to psychiatric disorders (6.3% vs. 4.3%) were generally similar between the treatment groups. No adverse events related to drug abuse or misuse were reported during the DB Phase.

In general, no clinically significant trend in vital signs, body weight, laboratory values, or electrocardiogram (ECG) parameters was observed in either group. However, consistent with the known pharmacologic effects of stimulant agents; the adverse events of weight decreased (7.0% for OROS methylphenidate HCl vs. 0% for placebo), transient increase in mean pulse rate from baseline (change: 9.2 bpm for OROS methylphenidate HCl vs 1.3 bpm) were higher in the OROS methylphenidate HCl group. For the QT interval corrected for heart rate using linear derived method (QTcLD) and linear corrected QT method (QTLc), no subject had a QTc value of >450 msec in either treatment group at end point. For the QT interval corrected for heart rate using the Bazett formula (QTcB), 4 subjects (2.8%) in the OROS methylphenidate HCl group and 3 subjects (2.2%) in the placebo group had a QTc value of >450 to 480 msec at endpoint. For the QT interval corrected for heart rate using the Fridericia formula (QTcF), 1 subject (0.7%) in the OROS methylphenidate HCl group had a QTc value of >450 to 480 msec at endpoint. No apparent relationship was observed between steady-state plasma concentration of methylphenidate or its major metabolite α-phenyl-piperidine-acetic acid (PPAA) and the change in QTc from baseline after multiple dosing.

Patient-reported ratings for responses to questionnaires on sleep, appetite, abuse potential, and suicidal ideation and behaviour (Columbia-Suicide Severity Rating Scale [C-SSRS]) were assessed. Based on questionnaires on sleep, the percentage of sleep conditions rated “poor” decreased from baseline at each postbaseline assessment point in both treatment groups. Based on questionnaires on appetite, the percentage rated their appetite as “less than usual amount” increased to 37.8% in the OROS methylphenidate HCl group and 12.1% in the placebo group at the endpoint, but returned to 6.3% and 5.7%, respectively, at the end of the Post-study Phase. Based on questionnaires on abuse potential, no apparent drug abuse potential was found in the OROS methylphenidate HCl group compared to the placebo group. Based on the C SSRS, a few subjects (4.2% in the OROS methylphenidate HCl group, 2.9% in the placebo group) experienced treatment-emergent suicidal ideation, while none experienced any treatment-emergent suicidal behaviour, compared to all prior history.

Conclusion: The results of this study indicate that OROS methylphenidate HCl (JNS001) in a dose range of 18 to 72 mg per day was effective and well-tolerated in the treatment of ADHD in Japanese adult subjects. No clinically important safety signals were observed for JNS001 compared with placebo.

7.1.2. JNS001-JPN-A02

Title of Study: An Open-Label, Dose-Titration, Long-Term Study to Evaluate the Safety of JNS001 in Adults with Attention-Deficit/Hyperactivity Disorder at Doses of 18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg, or 72 mg per day.[5]

Study Period: 02 May 2011 (first subject informed consent date) to 28 March 2013 (last observation date of last subject), Database lock date: 07 May 2013.

Primary Objective: The primary objective of this study was to evaluate the long-term safety and tolerability of JNS001 (OROS methylphenidate HCl) titrated to daily doses of 18 to 72 mg in adults with ADHD. Safety was to be evaluated based on AE reporting, vital signs, and clinical laboratory tests.

Methodology: This was a multicentre, open-label, dose-titration, long-term safety study in adult subject with a diagnosis of ADHD based on DSM-IV-TR. The study consisted of a 48-week Long-term phase (4-week titration period and 44-week maintenance period) and a 1-week Post-study phase. Subjects who had completed the preceding study (JNS001-JPN-A01, which consisted of an 8-week double-blind placebo-controlled phase and a 1-week Post-study phase) were eligible for this extension study to continue JNS001 treatment. Subjects were titrated from a starting dose of 18 mg per day for 7 days, and continued with weekly increments (+/- 2 days) of 9 or 18 mg per day until an individualised dose was achieved. During the maintenance period, the dose was adjusted between 18 to 72 mg per day depending on the subjects' symptoms. Safety was evaluated throughout the study and efficacy evaluations were performed at baseline and at designated time points in the Long-term phase. The Post-study phase was held for all subjects who received study treatment including those discontinued from the study.

Criteria for Evaluation: The efficacy assessments included the CAARS-O:SV: Total score, DSM-IV ADHD Symptom scales, and ADHD Index, CAARS-S:SV: Total score, DSM-IV ADHD Symptom scales, and ADHD Index, CGI-S score, CGI-C score, and Q-LES-Q-SF total score.

Safety assessment was based on reported AEs, clinical laboratory tests, vital sign and body weight measurements, ECG, evaluations of sleep, appetite, and abuse potential, and the C-SSRS.

Results:

Study Population: Of 254 eligible subjects who were enrolled in the study, 253 received at least 1 dose of study drug and had both baseline and post-dose efficacy data. These subjects were included in the full analysis set and the safety analysis set.

[5] Clinical Study Report JNS001-JPN-A02. An open-label, dose-titration, long-term study to evaluate the safety of JNS001 in adults with attention-deficit/hyperactivity disorder at doses of 18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg or 72 mg per day. Document ID No.: EDMS-ERI-74099089; Janssen Pharmaceutical K.K. (06 August 2013).

Of the 253 treated subjects, 205 subjects (81.0%) completed the Long-term phase, and 48 subjects (19.0%) discontinued study treatment in the Long-term phase. The most common reasons for discontinuation were adverse event (22 subjects) and withdrawal of consent (11 subjects).

At the entry of the preceding JNS001-JPN-A01 study, the subjects' age ranged from 18 to 58 years, with a mean age of 33.9 years. The age of subjects at initial ADHD diagnosis ranged from 1 to 58 years, with a mean age of 32.1 years. All of the subjects met the diagnostic criteria for ADHD according to DSM-IV-TR at present and in childhood based on CAADID.

Within 3 months prior to screening in the preceding JNS001-JPN-A01 study, 14.2% of the subjects (36/253) received 1 or more psychotropic agents for ADHD. The most commonly used psychotropic agents for ADHD were atomoxetine hydrochloride (12 subjects) and pemoline (10 subjects). During the Long-term phase, 22.1% of the subjects (56/253) received hypnotics or antianxiety drugs, and 7.9% of the subjects (20/253) psychotropic agents.

The mean duration of exposure to OROS methylphenidate HCl (including days with missed intakes) was 296.6 days. Most of the subjects received OROS methylphenidate HCl for at least 253 days. The dose distributions remained similar on any study visit day after Week 8, and the doses did not increase with extended treatment durations.

Efficacy Results:

The secondary objective of this study was to evaluate the long-term maintenance of efficacy of OROS methylphenidate HCl titrated to daily doses of 18 to 72 mg in adults with ADHD. The primary efficacy parameter was DSM-IV Total ADHD Symptoms scores, 1 of the subscale scores of CAARS-O:SV. The other efficacy parameters included CAARS-O:SV Total score and subscale scores other than DSM-IV Total ADHD Symptoms scores, CAARS-S:SV Total score and subscale scores, CGI-S, CGI-C, and Q-LES-Q-SF total score.

The baseline mean (SD) DSM-IV Total ADHD Symptoms scores of CAARS-O:SV were 31.8 (6.32). The mean DSM-IV Total ADHD Symptoms scores had decreased from baseline at Week 4, Week 12, Week 36, and end point (LOCF), with a mean change (SD) of -14.6 (8.72), -15.5 (9.37), and -16.1 (9.83), -16.7 (9.81), and -17.2 (9.91), respectively. A rapid decrease from baseline in the mean DSM-IV Total ADHD symptoms scores was observed during the 4-week titration period and then the decrease was generally maintained throughout the Long-term phase. This indicates that the efficacy of OROS methylphenidate HCl for improvement of ADHD symptoms was maintained over a long period. Similar improvement in DSM-IV Total ADHD Symptoms scores of CAARS-O:SV was achieved regardless of whether subjects received placebo or JNS001 in the preceding JNS001-JPN-A01 study.

The results of the other efficacy parameters consistently supported the long-term maintenance of efficacy of OROS methylphenidate HCl in adult subjects with ADHD. OROS methylphenidate HCl also reduced the severity of both inattentive symptoms and hyperactive-impulsive symptoms, as shown by a consistent marked improvement in the CAARS-O:SV "Inattentive symptoms" and "Hyperactive-Impulsive symptoms" subscales. The

mean change (SD) from baseline in CAARS-O:SV other subscale scores at end point (LOCF) was -11.1 (6.24) for "Inattentive symptoms" and -6.1 (5.23) for "Hyperactive-Impulsive symptoms".

In addition, the subject-rated CAARS-S:SV scale and the investigator-rated CGI-S and CGI-C scales also revealed a long-term effect of OROS methylphenidate HCl in reducing the severity of ADHD symptoms. The mean change (SD) from baseline in CAARS-S:SV DSM-IV Total ADHD symptoms scores and Total score was -14.6 (11.56) and -24.5 (19.24), respectively, at end point (LOCF). For the CGI-S scale, the percentage of subjects assessed as "moderately ill" or worse had decreased from 95.3% (241/253) at baseline to 26.5% (67/253) at end point (LOCF). For the CGI-C scale, the percentage of subjects who were assessed as "much improved" or "very much improved" was 64.8% (164/253) at end point (LOCF). There was a slight improvement in daily functioning based on Q-LES-Q-SF total scores, from baseline to end point (mean change: 2.5).

The dose distributions remained similar on any study visit day after Week 8. The doses did not tend to increase with extended treatment durations, and the effects based on the scales including CAARS-O:SV did not decrease. Therefore, there was no indication of tolerance to the therapeutic effects of the study drug for up to 48 weeks.

These efficacy results indicate that the therapeutic effect of OROS methylphenidate HCl at a dosage range of 18 to 72 mg per day was maintained during long-term treatment of ADHD in Japanese adult subjects.

Safety Results:

During the Long-term phase, 239 subjects (94.5%) experienced at least 1 AE. Drug-related AEs were reported in 179 subjects (70.8%). All of the AEs were mild or moderate in severity except 1 severe psychotic disorder (SAE), 1 severe deafness neurosensory (non-SAE), and 1 severe diverticulum intestinal (SAE). The most commonly reported drug-related AEs (≥5% of subjects) were decreased appetite (30.0%), weight decreased (19.4%), palpitations (15.8%), nausea (13.8%), insomnia (13.0%), thirst (10.3%), headache (9.1%), and tachycardia (7.1%). More subjects experienced AEs during the first 12-week period (including 4-week titration period) in this study. During Weeks 1 to 12, decreased appetite, insomnia, thirst, weight decreased, and palpitations were observed more frequently (difference of ≥5%) in subjects who were assigned to the placebo group in the preceding study than in those who were assigned to the OROS methylphenidate HCl group in the preceding study. During the Long-term phase, adverse events were reported in 91.1% of male subjects and 97.7% of female subjects. AEs that occurred more frequently in females than males (difference of ≥5%) were decreased appetite, insomnia, nausea, weight decreased, musculoskeletal stiffness, headache, nasopharyngitis, thirst, palpitations, and abdominal pain upper.

No deaths occurred in this study. Four other SAEs were reported during the study. During the Long-term phase, 3 SAEs were psychotic disorder in 2 subjects and diverticulum intestinal in 1 subject. Psychotic disorder was considered by the investigator to be probably or possibly related to the study drug, while diverticulum intestinal was considered not related to the study

drug. During the Post-study phase, 1 SAE (pyrexia) was reported in 1 subject who permanently discontinued study treatment due to a non-serious AE (headache) during the Long-term phase. The event was considered not related to the study drug by the investigator.

During the Long-term phase, 22 subjects (8.7%) permanently discontinued the study drug due to at least 1 AE. The most commonly reported AE leading to study drug discontinuation was palpitations, which was observed in 4 subjects (1.6%). Other AEs leading to study drug discontinuation were observed in 1 or 2 subjects, except for nausea (3 subjects).

Analysis of selected AEs of special interest showed that AEs related to decreased appetite, weight decreased, and growth (41.1%), AEs related to cardiovascular disorders (21.7%), and AEs related to initiating or maintaining sleep (19.4%) had been commonly observed. The AEs related to psychiatric disorders (7.1%) were relatively infrequent. No AEs related to drug abuse or misuse were reported during the Long-term phase.

During the Post-study phase, 16 subjects (6.3%) experienced at least 1 AE. Two subjects (0.8%) experienced drug-related AEs. Delirium, headache, hypoesthesia, and oropharyngeal pain were observed in the same subject mentioned above who experienced 1 SAE of pyrexia during the Post-study phase. All other AEs reported in the Post-study phase was observed in 1 subject, except for nasopharyngitis (3 subjects), malaise (2 subjects), and weight increased (2 subjects). The adverse events during the Post-study phase were evaluated for possible symptoms of withdrawal. None of the adverse events were reported in 3 or more subjects except nasopharyngitis, which suggests that after discontinuation of treatment there were no adverse events that would be indicative of a withdrawal phenomenon.

During the Long-term phase, 6 or fewer (≤ 2.4%) subjects experienced laboratory-related AEs. In general, no clinically significant trends in vital sign and body weight measurements, laboratory values, and ECG parameters were observed. Weight decreased was reported as an AE in 20.6% of the subjects during the Long-term phase, but none were reported during the Post-study phase. An increase in mean pulse rate from baseline was observed at end point (change: 7.3 bpm). The change from baseline tended to decrease, and the mean increase in pulse rate was 3.4 bpm at the end of the Post-study phase. No ECG findings were reported as an AE except 3 abnormalities (electrocardiogram QT prolonged, tachycardia, and palpitations).

Based on questionnaires on sleep, the percentage of sleep conditions rated “poor” decreased from baseline at each post-dose assessment point. Based on questionnaires on appetite, the percentage of subjects that rated their appetite as “less than usual amount” increased from 4.7% (12 subjects) at baseline to 19.8% (50 subjects) at end point, but returned to near baseline, 6.4% (16 subjects), at the end of the Post-study phase. Based on questionnaires on abuse potential, no apparent drug abuse potential was found in the OROS methylphenidate HCl treatment. Based on the C-SSRS, a minority of subjects (12 subjects, 4.8%) experienced treatment-emergent suicidal ideation during the Long-term phase, compared to all prior history. No subjects experienced any treatment-emergent suicidal behaviour during the Long-term phase.

Although several AEs such as decreased appetite, weight decreased, and palpitations were frequently reported in OROS methylphenidate HCl treatment as expected, no other safety signals or concerns were identified. In this study, there were no adverse findings that were unexpected from the findings in other paediatric or adult ADHD studies of MPH. Long-term treatment with JNS001 (titrated at weekly intervals in 9 or 18 mg increments up to a maximum of 72 mg/day) was generally safe and well tolerated by Japanese adult subjects with ADHD.

Conclusion: The results of this long-term safety study indicate that OROS methylphenidate HCl (JNS001) at a dose range of 18 to 72 mg per day was generally safe and well-tolerated in the treatment of ADHD in Japanese adult subjects. No clinically important safety signals were observed during long-term treatment with OROS methylphenidate HCl. The ADHD symptoms began to improve from the 4-week titration period, and the efficacy of JNS001 was maintained throughout the Long-term phase.

Based on review of the data from the 2 completed clinical trials of OROS methylphenidate HCl included in this report, there have been no important emerging efficacy and safety findings identified.

7.2. Ongoing Clinical Trials

There were no OROS methylphenidate HCl interventional studies that were on-going during the PBRER/PSUR reporting period.

7.3. Long-Term Follow-up

No long-term follow-up information became available during the reporting period.

7.4. Other Therapeutic Use of Medicinal Product

No pre-approval patient access programmes are ongoing for OROS methylphenidate HCl.

7.5. New Safety Data Related to Fixed Combination Therapies

This section is not applicable as OROS methylphenidate HCl is not administered in any fixed-combination therapies.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

Two OROS methylphenidate HCl non-interventional studies that were on-going during the PBRER/PSUR reporting period are presented in Table 15 (see also Appendix 5).

Table 15: OROS MPH Non-interventional Study Ongoing Within the Reporting Period

Protocol	Title	Objective	FPI and LPLV dates (if available)	Number of Subjects Exposed to OROS MPH
CONCERTAATT4101[a]	Remission Rate and functional outcomes during 6-momth's treatment of OROS MPH for Children With Attention Deficit Hyperactivity Disorder	To evaluate the remission rate and to compare cognitive/social functioning outcomes between remission and non-remission patients in a multi-centre sample of ADHD children treated with OROS-MPH.	FPI: 10 September 2010 LPLV: 10-March-2012	239
CON-KOR-5026 (CONCERTAATT4107)	52-Week Observational Study to Investigate Patients' Response to ADHD Pharmacotherapy and Factors Associated with Treatment Adherence in Korean Children and Adolescents with ADHD	This is a 1-year open-label, multicenter, single arm, prospective, observational study to explore under natural setting the efficacy of drug treatment in children and adolescents diagnosed with ADHD according to DSM-IV and interview using K-SADS-PL. After obtaining informed consent, investigator will prescribe stimulant or non-stimulant ADHD treatment medications (i.e. IR/ER/OROS methylphenidate, atomoxetine). Efficacy and safety assessments will be performed 4, 12, 24, 36, and 52 weeks after the first day of study drug administration. Progression of symptom improvement and adherence will be investigated and associated variables (i.e. demographic, clinical, familial and treatment factors) will be analysed. An estimated 276 subjects are planned to be enrolled.	FPI: 01 February 2012 Expected LPLV: 28-March-2014	245

Key: ADHD= Attention Deficit Hyperactivity Disorder, DSM-IV= Diagnostic and Statistical Manual of Mental Disorder; ER= Extended release; FPI= First patient in, IR= Immediate release; K-SAD-PL= Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; LPLV= Last patient last visit, MPH= Methylphenidate hydrochloride

a: No study subjects were exposed during the report period; the CSR was issued on 10 December 2013.

SAFETY RESULTS CONCERTAATT4101:

There were no treatment emergent deaths or serious adverse events (SAEs). A total of 13 (5.4%) subjects and 16 (6.7%) subjects experienced TEAEs that led to study drug discontinuation during 8 weeks and 24 weeks, respectively. The most frequently reported (observed in ≥3% of the total subjects) TEAEs included decreased appetite (27.2% and 30.1% during 8 weeks and 24 weeks, respectively), sleep disorder (10.5% and 10.9% during 8 weeks and 24 weeks, respectively), initial insomnia (7.5% and 8.4% during 8 weeks and 24 weeks, respectively), nausea (4.2% and 4.6% during 8 weeks and 24 weeks, respectively), abdominal pain (4.2% each, during 8 weeks and 24 weeks), vomiting (3.3% and 3.8% during 8 weeks and 24 weeks, respectively), and tachycardia (3.3% during 24 weeks).

Based on review of the data from these ongoing non-interventional studies for OROS methylphenidate HCl included in this report during this reporting period, no new information with potential impact to the benefit-risk assessment has been identified (see Appendix 5).

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

No safety information from other clinical trials and sources became available during this reporting period.

9.2. Medication Errors

Cases of medication errors are reviewed in Section 16.2.5.2, Medication Error/Maladministration.

10. NON-CLINICAL DATA

No non-clinical trials were conducted during the reporting period.

11. LITERATURE

A search of the scientific literature using multiple databases, including MEDLINE, Derwent Drug File, Biosis, and Embase, was performed to capture safety information involving OROS methylphenidate HCl for the period of this PBRER/PSUR. Abstracts, as published, that contained relevant safety information, are presented below.

Poulton AS, Melzer E, Tait PR, et al. Growth and pubertal development of adolescent boys on stimulant medication for attention deficit hyperactivity disorder. *Med J Aust* 2013: 198(1): 29-32

OBJECTIVE: To investigate the growth and pubertal attainment of boys with ADHD on stimulant medication.

DESIGN, SETTING AND PARTICIPANTS: Longitudinal study of boys aged 12.00-15.99 years at recruitment in 2005-2011, with stimulant-treated ADHD for at least 3 years, attending three paediatric practices (subjects), compared with longitudinal data from 174 boys from the Nepean longitudinal study (controls).

MAIN OUTCOME MEASURES: Subjects' growth parameters before treatment were compared with controls aged 7 or 8 years; growth parameters and longitudinal changes on treatment to ages 12.00-13.99 and 14.00-15.99 years were compared with controls reviewed at 13 and 15 years of age, respectively. The subjects' pubertal staging and height velocity were related to their treatment history.

RESULTS: Sixty-five subjects were recruited; mean duration of treatment was 6.3 +/- 1.9 years. At baseline, their growth parameters were not significantly different from those of the controls after adjusting for age. Compared with the controls, after adjusting for current age and baseline growth parameter z score, subjects aged 12.00-13.99 years had significantly lower weight and body mass index ($P<0.01$), and those aged 14.00-15.99 years had significantly lower height and weight ($P < 0.05$). At 12.00-13.99 years of age, the subjects were comparable to the controls in their pubertal development adjusted for age, but those aged 14.00-15.99 years reported significant delay (mean Tanner stage, 3.6 for subjects v 4.0 for controls; $P<0.05$). The dose of medication was inversely correlated with the height velocity from baseline to 14.00-15.99 years of age ($P<0.05$).

CONCLUSIONS: Prolonged treatment (more than 3 years) with stimulant medication was associated with a slower rate of physical development during puberty. To maintain adequate height velocity during puberty, we recommend keeping the dose as low as possible.

MAH Commentary: The purpose of this longitudinal study was to investigate the effect of stimulant medication on growth and pubertal development in boys between the ages of 12 and 16 years of age. The patients were required to have had stimulant treatment for at least 5 years and the controls were from the Nepean longitudinal study. The boys aged 12-13.99 years of age that received stimulant medication were noted to have decreased weight but comparable growth in height and pubertal development to controls. However, boys aged 14 to 15.99 were considerably behind controls in their height and pubertal development, suggesting that stimulant medication during puberty delays the rate of growth velocity including the timing of peak height velocity but does not delay the onset of puberty. The Company will continue to monitor events of decreased growth in relation to patient age & pubertal development.

12. OTHER PERIODIC REPORTS

This section is not applicable.

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting period, no information relevant to lack of efficacy from controlled clinical trials was received for OROS methylphenidate HCl.

14. LATE-BREAKING INFORMATION

Since the data-lock point of 31 October 2013, the following previously unrecognised ADRs with OROS methylphenidate hydrochloride were identified:

- Priapism
- Increased Libido

Refer to Section 16, Signal and Risk Evaluation.

15. OVERVIEW OF SIGNALS: NEW, ONGOING, OR CLOSED

The objective of the GMS safety signal detection programme is to review safety data from multiple sources using multiple signal detection methodologies, in order to proactively detect patterns in AE reporting that might suggest new or emerging safety concerns.

Overview of Data Sources

Signal detection is performed on all Individual Case Safety Report (ICSR) data in the Company safety database for a product. Signal detection activities include both individual medical assessment as cases are received and periodic aggregate reviews of ICSR data by spontaneous and non-spontaneous report source. Additionally external databases, such as the United States Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) and Spontaneous Reporting System (SRS) or the WHO VigiBase, may be data mined on a periodic basis.

Overview of Signal Detection Methods

Single Case Assessment

ICSRs are reviewed as they are received and entered into the GMS safety database. The analysis may also include the retrospective review of ICSRs. During this process, events in single cases or a temporal cluster of single cases may be identified that require further evaluation.

Aggregate Safety Analysis of Spontaneous Data

Routine aggregate signal detection practices for post-marketing spontaneous reports include the periodic surveillance of AE reports irrespective of country of origin, seriousness, medical confirmation, or validity. This programme includes the following activities:

- Intra-Product (within product) Signal Detection Review of Spontaneous Data

  Ongoing periodic reviews of aggregate post-marketing spontaneously reported safety data in the GMS safety database and applicable legacy safety databases to identify relevant changes in reporting frequency or patterns of AEs, AE groupings, and AEs by lot for a Company product over time that may suggest potential safety and/or product quality signals.

- Inter-Product (between products) Signal Detection Review (ie, Data Mining)

  A cumulative review that screens large electronic safety databases such as the US FDA SRS/AERS, WHO Vigibase, and/or internal databases, such as the GMS safety database, to identify AEs reported disproportionately for a product of interest relative to other products in the database.

Aggregate Safety Analysis of Non-Spontaneous Data

The review of non-spontaneous AE data in the GMS safety database, such as interventional clinical trial SAE cases (including any non-serious events reported as part of SAE reporting) and non-interventional clinical trial cases (including solicited, registry or epidemiology studies), is conducted on a regular basis. All the relevant non-spontaneous data for a product in a review period are aggregated, allowing a review of data across clinical trials and/or indications.

Signal Management

Findings from signal detection reviews are communicated with appropriate functional groups and at appropriate forums within the Company. If the findings are consistent with a new or emerging safety and/or quality concern, further evaluations and/or actions are conducted by relevant functional groups within the Company as appropriate. These may include, but are not limited to, additional investigation and evaluation, revision of the CCDS and/or notification of applicable health authorities. Additionally, findings from any of these reviews are discussed in the PBRER/PSUR as warranted.

A tabulation of validated signals ongoing and closed during the reporting interval can be found in Appendix 6, Interval Tabular Summary of Safety Signals.

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Introduction

Important identified and potential safety concerns at the beginning of the current reporting period for OROS methylphenidate HCl are described in the current EU-RMP dated 10 December 2012, as well as, in Section 16.4.

OROS methylphenidate HCl is generally well tolerated.

After the period of this update, the following previously unrecognised ADRs with OROS methylphenidate hydrochloride were identified:

- Priapism
- Increased Libido

16.2. Signal Evaluation

Identified Risks: Priapism; Libido Increased

After the period of this update, the following previously unrecognised ADRs with OROS methylphenidate hydrochloride were identified:

- Priapism
- Increased Libido

Based upon a review of relevant non-clinical, clinical, epidemiologic information, scientific literature and post marketing data for OROS methylphenidate HCl, priapism and increased libido were identified as risks.

On 09 October 2013, the Company received a Prior Approval Supplement (PAS) request from the US Food and Drug Administration (FDA) for the addition of priapism and libido changes to the CONCERTA® US Package Insert. As the current OROS methylphenidate HCl CCDS lists libido decreased as an adverse drug reaction (ADR), decreased libido was not reviewed further.

All post-marketing and clinical trial cases of priapism and increased libido found in the GMS database, in patients treated with OROS methylphenidate HCl were reviewed to determine if there is a drug-event association between OROS methylphenidate HCl use and the occurrence of priapism and increased libido.

A cumulative search of the GMS database was performed for cases of OROS methylphenidate HCl received through 17 October 2013, and coded to the following Medical Dictionary for Regulatory Activities (MedDRA; version 16.0) High Level Terms (HLTs): Erection & ejaculation conditions and disorders and Sexual function and fertility disorders NEC.

Additionally, an integrated search of major biomedical literature databases was performed for all available literature relating to methylphenidate and priapism, libido changes. The FDA adverse event reporting system (FAERS) was also searched for cases involving the use of methylphenidate products and priapism, libido increased, libido decreased, and loss of libido.

The search retrieved 161 cases. Of these 161 cases, 125 cases were coded to Preferred Terms (PTs) not specifically related to priapism, libido increased/libido disorder, or were coded to the PT Libido decreased, which is listed as an ADR in the CCDS for OROS methylphenidate HCl. As a result, these cases were not reviewed further. The remaining 36 cases were categorized into those related to priapism (25 cases) and libido increased/ libido disorder (11 cases).

The majority of the 36 cases were reported from the US (33%; 12/36) and most cases involved male patients (83%; 30/36), which is consistent with what is reported in the literature. A majority of the priapism cases involved patients' ≤17years (88%; 22/25), while most increased libido cases involved patients between 36 to 50 years of age (36%; 4/11).

Of the 25 priapism cases, 13 cases had confounding factors or lacked sufficient information for assessment. Four additional cases were determined to be not likely related to OROS methylphenidate HCl use upon case level evaluation. Of the remaining 8 cases, 4 cases reported a positive dechallenge, 2 cases reported a positive dechallenge and rechallenge and 2 cases reported priapism during a drug holiday with the event resolving only after the patient was administered OROS methylphenidate HCl.

There were 4 cases presented in the FDA PAS request along with 11 cases retrieved via the GMS database search related to libido increased/libido disorder. Of the 4 FDA cases, 1 case reported a positive dechallenge and rechallenge, 1 case reported that the dose was not changed and the event did not resolve, and 2 cases lacked sufficient information for assessment.

A review of the literature identified 5 articles that referenced priapism or libido changes with methylphenidate use. One of the 5 articles described a case report of priapism. The 4 remaining articles included 2 clinical trials and 2 review articles; all of which detailed the use of methylphenidate and a possible association with libido changes.

The FAERS data mining results for generic methylphenidate, methylphenidate sustained release and methylphenidate extended release products demonstrated that methylphenidate sustained release had a slightly elevated signal score for PT Priapism while methylphenidate and methylphenidate extended release had a slightly elevated signal score for PT Libido increased.

Based on the findings detailed above, the Company concluded the cumulative weight of evidence was sufficient in supporting both priapism and increased libido as risks associated with the use of OROS methylphenidate HCl. Evaluation of these risks is ongoing.

These signals do not alter the overall favourable benefit risk profile of OROS methylphenidate HCl.

False Signal - Cardiomyopathy

Based on review of the results from non-clinical, clinical, epidemiologic information and scientific literature and post marketing data for OROS methylphenidate HCl the following signal has been rejected as a false signal:

- Cardiomyopathy.

Cardiomyopathy was identified as a potential safety signal for methylphenidate HCl based on an article in a Swedish non-peered reviewed medical magazine by Wikström et al which described 5 cases of cardiomyopathy in patients treated with a ADHD medication; in 2 of the 5 cases the patients reported receiving OROS methylphenidate HCl. A review was conducted of cumulative post-marketing and clinical trial cases reporting cardiomyopathy with the use of OROS methylphenidate HCl and entered into the GMS safety database.

The GMS safety database search was performed for all medically confirmed cases received cumulatively through 18 September 2013 involving the use of OROS methylphenidate HCl and adverse events coded to Preferred Terms (PTs) included in the Medical Dictionary for Regulatory Activities (MedDRA version 16.0) Standard MedDRA Query (SMQ) Cardiomyopathy (narrow).

Additionally, an integrated search of major biomedical literature databases was performed for all available literature relating to methylphenidate and cardiomyopathy. The Food and Drug Administration adverse event reporting system (FAERS) was also searched for reports of cardiomyopathy involving the use of CONCERTA® and other methylphenidate-containing products.

The GMS database search revealed 18 cases. Twelve cases were eliminated from further review due to insufficient information or confounding factors. The majority of cases were reported from Nordic countries and the majority of patients were between 18 and 35 years of age. Of the remaining 6 cases, only 1 case did not have any factors confounding the assessment. There were no positive dechallenge or rechallenge cases.

FAERS data mining results for OROS methylphenidate HCl and other methylphenidate products showed a slightly elevated signal score for the PTs Cardiomyopathy and Congestive cardiomyopathy.

A literature search did not identify additional evidence of an association between methylphenidate and cardiomyopathy. The literature review identified an FDA Paediatric Advisory Committee report in June 2005, which summarized post-marketing cardiac reports in children receiving methylphenidate-containing products. The report concluded that the review did not determine whether cardiovascular events in patients on stimulants were causally related. In 2006, a FDA Paediatric Advisory Committee reviewed 11 cases of sudden death reported between 1992-2005 in patients on methylphenidate or amphetamines.[6] The committee recommended that the labels of methylphenidate and amphetamine labels be updated to indicate stimulant-related deaths in patients with heart problems have been reported. In addition, they recommended labels advise against using these products in individuals with known serious structural abnormalities of the heart, cardiomyopathy, or serious heart rhythm abnormalities.[7] Additional articles focused on the cardiovascular safety of stimulants, sudden cardiac death, patient screening and monitoring, and updated guidelines. One review article assessed 15 controlled studies using test doses of methylphenidate in previously unmedicated children and found no consistent or clinically meaningful changes in blood pressure and no ECG irregularities concluding that it is probably not essential to monitor heart rate, blood pressure, or ECG prior to or during the use of stimulants, unless there are comorbid cardiovascular abnormalities.[8]

[6] Manos MJ, et al. Changes and challenges: Managing ADHD in a fast-paced world. *J Managed Care Pharmacy 2007*

[7] Ella J, Vetter V. Cardiovascular Effects of Medications for the Treatment of Attention-Deficit Hyperactivity Disorder: what is known and how should it influence prescribing in children? *Pediatr Drugs*. 2010;12(3);165-175.

[8] Safer DJ. Relative cardiovascular safety of psychostimulants used to treat attention-deficit hyperactivity disorder. J *Clin Adolesc Psychopharmacol*. 1992;2(4):279-290.

In another large study, there was no evidence that current use of ADHD medications was associated with an increased risk of serious cardiovascular events.[9,10] Other studies concluded that stimulant medications appear to be associated with sudden death, although rare, but do not change the risk-benefit profile. Several articles discussed the importance of a thorough review of medical history to include specific cardiac symptoms (ie, palpitations, near syncope, and syncope), Wolf-Parkinson-White syndrome, sudden death in the family, hypertrophic cardiomyopathy, and long QT syndrome prior to treatment with stimulants because pre-existing cardiac disease may be a factor in the development of cardiomyopathy in patients taking MPH.[11,12] These articles also suggest that an ECG prior to treatment with stimulants may increase the likelihood of identifying significant cardiac conditions such as hypertrophic cardiomyopathy.

The current Company Core Data Sheet (CCDS; version 15 May 2012) does not list cardiomyopathy as an adverse drug reaction (ADR). The CCDS Warnings & Precautions section states the following regarding the use of OROS methylphenidate HCl in patients with structural cardiac disorders:

"Warnings and Precautions: Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities."

Based on the cumulative weight of evidence the Company concluded there is insufficient evidence to support cardiomyopathy as an adverse drug reaction associated with the use of OROS methylphenidate HCl. Based on this review, cardiomyopathy was considered a false signal and closed.

Ongoing Signal Evaluation: Hearing Loss

The following signal is currently being evaluated to determine if it is a signal for OROS methylphenidate HCl:

- Hearing loss

Hearing loss was identified as a safety signal for OROS methylphenidate HCl, based on an updated clinical study report in Japan. Janssen Pharmaceutical Kabushiki Kaisha (JPKK) added hearing loss to the OROS methylphenidate HCl Japan PI as an "Other Adverse Drug Reaction

[9] Cooper WO, Habel LA, Sox CM et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896-1904.

[10] Habel LA, Cooper WO, Sox CM, et al. ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults. *JAMA*. 2011;306(24):2673-2683.

[11] Donnelly CL, Reimherr FW, Young JL. Differential diagnosis and treatment of Adult ADHD and Neighboring Disorders. *CNS Spectrums*. 2006;11(Suppl 11):1-12.

[12] Vetter VL, Elia J, Erickson C,et al. AHA Scientific Statement. Cardiovascular Monitoring of Children and Adolescents with Heart Disease Receiving Medications for Attention Deficit/Hyperactivity Disorder. *Circulation*. 2008;117:2407-2423.

(ADR)" after 3 non-serious cases relating to hearing loss in adult patients were reported. Events are added to the ADR table in the Japan PI when 3 or more cases are reported in clinical trials.

The Company is in the process of evaluating whether hearing loss is associated with OROS methylphenidate HCl. This evaluation will include a cumulative search of the GMS database for all OROS methylphenidate HCl cases reporting adverse events coded to PTs included in the MedDRA version 16.0 SMQ Hearing impairment (narrow). Additionally, an integrated search of major biomedical literature databases will be performed for all available literature relating to methylphenidate and hearing loss. The Food and Drug Administration adverse event reporting system will also be searched for cases involving the use of OROS methylphenidate HCl and other methylphenidate products and events related to hearing loss.

The outcome of this review will be discussed in the next PBRER/PSUR.

16.2.1. Other Important Safety Topics

The following events/topics were selected for monitoring and discussion in this PBRER/PSUR period: Neoplasms, Benign, Malignant and Unspecified (Including Cysts and Polyps), Nervous System Disorders (Strokes and Cerebrovascular Events), and Psychiatric Disorders (Suicide and Self Injury).

16.2.1.1. Cases With Fatal Outcome

Introduction

Cases reporting a fatal outcome are reviewed in all PBRERs/PSURs.

Sudden death is listed as an important potential risk in the OROS methylphenidate HCl RMP. The Warning and Precautions Section of the OROS methylphenidate HCl CCDS states: "*Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities".* In addition, angina pectoris, bradycardia, extrasystoles, supraventricular tachycardia, and ventricular extrasystoles are listed events in the OROS methylphenidate HCl CCDS but not with a fatal outcome.

As part of a commitment detailed in the RMP for OROS methylphenidate HCl, the MAH continues to perform enhanced pharmacovigilance in the form of a targeted questionnaire to all reporters of sudden death.

Methods

Cases reporting a fatal outcome[13] are discussed regardless of listedness.

[13] Cases with a classification of "Death" or reporting selected PTs (see Appendix 7.1).

Results

During this reporting period, 15 medically confirmed cases[14] (12 initial, 3 follow-up) and no medically unconfirmed cases reporting a fatal outcome were identified. Of the medically confirmed cases, a review of the follow-up cases did not change the prior assessment of the event in 2 cases, including 1 received from the literature ([redacted]); therefore, these cases are not discussed further. The remaining follow-up [redacted] contained relevant new information (a change of fatal event) and is therefore included in the review with the initial cases. Three initial literature cases concerned multiple unidentifiable patients and contained minimal information: [redacted] (Completed suicide) concerned multiple patients with a history of depression who committed suicide, [redacted] (Sudden death) concerned multiple patients with ADHD and reported that the incidence of sudden death with OROS methylphenidate HCl was 0.2 for every 100,000 due to cardiac symptoms, and [redacted] (Pneumonia, Dyspnoea) reported that severe events like pneumonia and dyspnoea were resulting in death; no information such as dose or action taken was provided and these cases are not discussed further. One initial case [redacted] [Abortion spontaneous, Uterine dilation and curettage, Foetal death, Exposure during pregnancy]) reported a foetal death and is discussed in Section 16.3.5.1, Positive and Negative Experience During Pregnancy or Lactation.

Table 16 displays a count of the PTs of interest with fatal outcomes by age and seriousness in the remaining 9 cases received in the current PBRER/PSUR reporting period.

[14] [redacted]

[15] Schelleman H, Bilker WB, Kimmel SE, et al. Methylphenidate and risk of serious cardiovascular events in adults. *Am J Psychiatry* 2012;169:2:178-185.

[16] Kim HM, Smith EG, Ganoczy D, et al. Predictors of suicide in patient charts among patients with depression in the Veterans Health Administration health system: Importance of prescription drug and alcohol abuse. *J Clin Psychiatry* 2012; 73 (10): e1269e1275.

[17] Mendonca de Andrade CR, Parreiras da Silva WA, Ferreira Belizario Filho J, Cavalheiro da Silveira JC. Attention deficit hyperactivity disorder (ADHD). *Rev Med Minas Gerais* 2011;21/4:455-464.

[18] Lee WJ, Schumock GT, Lee TA. Drugs associated with adverse drug events in children: analysis of the United States FDA adverse event reporting system database. Value in Health ISPOR 18th Annual International Meeting New Orleans, LA United States 2013;16(3):A70.

Table 16: Interim Count of Selected PTs by Age and Seriousness in OROS MPH Cases Reporting Fatal Outcomes

Preferred Term	Number of Events[a,b,c]		
Age (years)	**<18[d]**	**≥18[e]**	**NR[f]**
Cardiac disorder	-	1	-
Completed suicide	-	3	-
Death	-	-	2
Drug abuse	-	1	-
Incorrect route of drug administration	-	1	-
Toxicity to various agents	-	5	-
Subtotal	**-**	**11**	**2**
Total	**13**		

Key: MPH= Methylphenidate hydrochloride; NR= Not reported, PT= Preferred term
a: Cases may have reported more than 1 event of interest.
b: Events reported from medically confirmed cases
c: Dash (-) indicates the specified PT was not identified within the age/age group.
d: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
e: Includes patients ≥18-years-old and/or patient age category: adult, elderly.
f: Includes patients with no reported age and age category.

Three initial cases, including 2 [redacted] reported the primary PTs of Completed suicide (3) and Toxicity to various agents (2). These cases are presented in Section 16.2.1.4, Depression and Suicide/Self Injury, and are not further discussed in this section.

Two cases received from [redacted] reported death due to a multiple drug overdose (Toxicity to various agents). It was reported that the patients took the overdoses in a suicide attempt (with methylphenidate HCl, paracetamol, buspirone, fluoxetine, nefazodone, and hyoscyamine) and suspected suicide attempt (with OROS methylphenidate HCl, venlafaxine, hydroxyzine, buspirone, trazodone, and bupropion), respectively. It was not reported if either patient was prescribed OROS methylphenidate HCl. Medical history was not reported.

[redacted] (Toxicity to various agents, Drug abuse, Incorrect route of drug administration) from the same article, reported that [redacted] ingested OROS methylphenidate HCl parenterally (unspecified formulation) along with the co-suspect drugs oxycodone, diazepam, and cocaine with an intent of abuse. The patient died from multiple drug toxicity on an unspecified date. Oxycodone (free) level in blood was 190 ng/mL (no further laboratory results were provided). OROS methylphenidate HCl was causally ranked 1.

[19] Bronstein AC, Spyker DA, Cantilena LR Jr., et al. 2011 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS): 29th Annual Report. *Clin Toxicol* (2012);50: 911-1164.

Two literature cases concerning patients of unspecified age and sex reported the single PT of Death. [redacted] reported that the patient died in a road accident; he was the driver of the car. A blood test revealed the presence of OROS methylphenidate HCl along with other unspecified drugs. No further information was provided. [redacted] reported that on an unspecified date, the patient died due to a drug-related death. An autopsy revealed methylphenidate HCl, tramadol, fluvoxamine, mirtazapine, quetiapine, nortriptyline, and sildenafil in the blood. No further information was provided.

The remaining [redacted] with a history of cocaine abuse, contained follow-up information to a previously reported sudden death. A medical history of tuberculosis sclerosis was ruled out. In the conclusion of the autopsy statement, it was "assumed that the cause of death was a consequence of the identified severe cardiac changes, coded as cardiac event (Cardiac disorder). Thus significant changes in the heart such as ARVC-like changes (arrhythmogenic right ventricular cardiomyopathy) as well as connective tissue and fat formation in the heart were identified." It could not be determined if the medication found in the blood, OROS methylphenidate HCl, had any importance for the death.

Discussion

A total of 9 cases were included for further review. [redacted] are reviewed in Section 16.2.1.4, Depression and Suicide/Self Injury. [redacted] reporting death due to suicide were confounded by multiple co-suspect medications. [redacted] reporting death associated with drug abuse was confounded by co-suspect cocaine, which has been associated with sudden deaths and cardiac arrest,[22] and oxycodone,[23] which may cause fatal respiratory depression when administered to opioid naive patients or if tablets are administered parenterally; lack of information including route of administration, medical history, and course of events precludes further assessment. [redacted] reporting the PT Death contained insufficient information regarding the fatal event; [redacted] reported that other unspecified medications were found in the patient's blood and [redacted] reported multiple co-suspect medications. In the remaining [redacted] the patient's underlying cocaine abuse, including a relapse 2 to 3 weeks prior to his death, likely contributed to the fatal cardiac event; people who use cocaine may suffer heart attacks or strokes.[22]

Conclusion

Based on the review of these cases, no changes to the CCDS are warranted at this time.

[20] Poulsen H, Moar R, Troncoso C. The incidence of alcohol and other drugs in drivers killed in New Zealand road crashes 2004-2009. *Forensic Sci Int* 2012;223(1-3):364-370.

[21] Lusthof KJ. Sildenafil related deaths in The Netherlands. *Clinical Toxicology* 2012;50(4):328.

[22] Drug facts: Cocaine. National Institute on Drug Abuse. http://www.drugabuse.gov/publications/drugfacts/cocaine. Accessed on 25 November 2013.

[23] Oxycodone. Electronic Medicines Compendium. http://www medicines.org.uk/emc/medicine/2579/SPC/OxyContin+tablets/. Accessed on 25 November 2013.

16.2.1.2. Neoplasms, Benign, Malignant and Unspecified (Including Cysts and Polyps)

Introduction

All PTs in this SOC are reviewed due to their medical significance. Carcinogenicity and Lymphocytic leukaemia are RMP potential risks associated with the use of methylphenidate containing products.

Methods

A frequency tabulation of MedDRA PTs reported for OROS methylphenidate HCl during the reporting period was reviewed to identify topics for review The following Standardised MedDRA Query (SMQ) was selected to identify cases for review: Malignant Tumours (Narrow). Additionally, all PTs in the SOC Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps) were selected. The GMS safety database was searched to retrieve medically confirmed cases reporting events in the SMQ and SOC.

Results

The search described above identified 5 cases[24] (3 initial, 2 follow-up). Of the 5 medically confirmed cases, a review of the 2 follow-up cases [redacted] did not change the prior assessment of the event in both cases; these cases are, therefore, not discussed further.

Table 17 displays a count of the selected PTs, all of which were serious and unlisted, by age and seriousness in the 3 remaining cases (all spontaneous reports) received for the current PBRER/PSUR reporting period.

Table 17: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Neoplasms, Benign, Malignant and Unspecified (Including Cysts and Polyps)

Preferred Term	Number of Events[c]	
Age (years)	**<18[a]**	**≥18[b]**
Benign hepatic neoplasm	1	-
Cyst	1	-
Pituitary tumour	-	1
Subtotal	**2**	**1**
Total	**3**	

Key: MPH= Methylphenidate hydrochloride; PT= Preferred term
a: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
b: Includes patients ≥18-years-old and/or patient age category: adult, elderly.
c: ash (-) indicates the specified PT was not identified within the age/age group.

Of the 3 cases included for further review, 2 involved adolescents. [redacted] involved a [redacted] with a history of a focal nodular hyperplasia (FNH) of the liver (Benign hepatic neoplasm), who experienced an increase in size of the tumour (5.5 to 10.5 cm) over a period of 3 months, which started approximately 2 to 3 months after commencing OROS methylphenidate HCl. The dosage was reduced and the patient recovered from the event.

[redacted]

The remaining 2 cases (involving 1 adolescent patient and 1 adult patient) are presented further below (PTs of interest are italicised).

Patients <18-years-old

- [redacted] **(Epilepsy, Arthralgia, Migraine, *Cyst*, Nausea, Dizziness):** This case involved [redacted] with a sleep problem who was treated with OROS methylphenidate HCl 36 mg daily for ADHD and high functioning autism. The patient's medical history and concurrent conditions were not reported. Concomitant medications included melatonin to help with sleep. An unspecified time after starting OROS methylphenidate HCl, the patient was seen in the emergency ward with nausea, dizziness, and joint pain. An atypical migraine was suspected. At the emergency ward a cyst was discovered on X-ray (possibly a skull X-ray). The patient was also recently diagnosed with epilepsy. Treatment with OROS methylphenidate HCl was withdrawn on an unspecified date, and the outcome of the events was not reported (see Section 16.3.5.2.4, Use in Children).

Patients ≥18 years-old

- [redacted] **(*Pituitary tumour*, Peyronie's disease, Hypogonadism):** [redacted] with a medical history of unspecified allergy, alcohol abuse, anxiety, arthritis, depression, disturbance in attention, fatigue, hypersensitivity, and osteoarthritis received treatment with OROS methylphenidate HCl 18 mg daily for fatigue and difficulty concentrating and focusing. Co-suspect medications included sertraline, clonazepam, and bupropion. The patient was on these medications approximately 4 years prior to this report, when he developed a pituitary gland tumour resulting in erectile dysfunction (described as loss of libido and Peyronie's disease). Treatment with sertraline and bupropion was withdrawn on an unspecified date. The dose of OROS methylphenidate HCl and clonazepam was not changed. The patient also experienced an increased loss of appetite over approximately 8 months[redacted] would eat once a day and then once every few days), hypogonadism, and low testosterone levels (testosterone was below 200 [units and normal range unspecified]) on unspecified dates. The patient stopped taking OROS methylphenidate HCl due to increasing loss of appetite. The outcome of the events was not reported. The reporter stated there was no probable correlation between the pituitary gland tumour, Peyronie's disease, hypogonadism, and OROS methylphenidate HCl.

Discussion

Patients <18-years-old

There were 2 cases received during the current review period involving paediatric patients. In [redacted] had a history of a benign hepatic tumour with focal nodular hyperplasia that progressed in size. The dose of OROS methylphenidate HCl was decreased and the patient recovered. FNH is very rare in paediatric population with age prevalence in children 7-8 years old, although some cases are diagnosed in early childhood or even in the prenatal period[25]. The female sex is predominant with a Male/Female ratio of less

[25] Lack EE, Ornvold K: Focal nodular hyperplasia and hepatic adenoma: a review of eight cases in the pediatric age group. *J Surg Oncol* 1986, 33:129-35.

than 1/10 in one of the largest series[26]. The cause is unknown although the hypothesis that obstruction of hepatic vessels or abnormal vascularization could account for FNH is suggested by the reported association with clinical and anatomic findings like hypoplasia or agenesis of the portal vein, vascular malformations, haemangioma and vascular dysplasia, Budd-Chiari syndrome and hereditary haemorrhagic telangiectasia. Focal nodular hyperplasia has been associated with a few drugs, such as oral contraceptives in females.[27]. More information is needed to determine the role of OROS methylphenidate HCl, if any, in the tumour progression followed by "recovery" after the dose was reduced. The reporter did not provide a causality assessment for the hepatic tumour progression. [redacted] dizziness and joint pain are due to the cyst; however, the lack of information relating to the patient's medical history, details relating to the cyst, such as location, and diagnostic tests, precludes further evaluation.

Patients ≥18-years-old

[redacted] treated for the off label indications of fatigue and difficulty in concentrating/focusing. The reporter did not consider the events of pituitary gland tumour, Peyronie's disease and hypogonadism to be related to treatment with OROS methylphenidate HCl. Pituitary tumours are common neoplasms and often result in gonadotrophin deficiency resulting in diminished libido, hypogonadism, and impotence.[28] The case was also confounded by the use of sertraline, which is known to cause sexual dysfunction in men and, rarely, neoplasms.[29]

Conclusion

Review of these cases does not provide evidence that represents a new safety concern. No changes to the CCDS are warranted at this time.

16.2.1.3. Nervous System Disorders: Strokes and Cerebrovascular Events

Introduction

Cerebrovascular disorders are identified as an important potential risk in the OROS methylphenidate HCl RMP. As part of a MAH Pharmacovigilance plan, enhanced pharmacovigilance (i.e., routine case follow-up with questions on the AE for cases reported with OROS methylphenidate HCl) continues to be performed for cerebrovascular events.

---

[26] Luciani A, Kobeiter H, Maison P, et al. Focal nodular hyperplasia of the liver in men: is presentation the same in men and women? *Gut* 2002;50:877-80.

[27] Rebouissou S, Bioulac-Sage P, Zucman-Rossi J: Molecular pathogenesis of focal nodular hyperplasia and hepatocellular adenoma**.** *J Hepatol* 2008;48:163-70.

[28] Pituitary Tumors. Available at: http://emedicine medscape.com/article/1157189-overview#a0101. Accessed 20 November 2013.

[29] Sertraline. Summary of Product Characteristics. http://www medicines.org.uk/emc/medicine/25805/SPC/Sertraline+100mg+Film+coated+Tablets/#UNDESIRABLE_EFFECTS. Accessed 20 November 2013.

The MHRA has requested that the MAH continue to monitor cerebrovascular AEs, including stroke and ischaemic events.

Methods

A frequency tabulation of MedDRA PTs reported for OROS methylphenidate HCl during the reporting period was reviewed to identify topics for review. The following MedDRA SMQ was selected to identify cases for review: Cerebrovascular disorders (Broad). The GMS safety database was then searched to retrieve medically confirmed cases reporting PTs within the SMQ.

Results

The search identified 8 medically confirmed cases[30] (6 initial, 2 follow-up) received during the reporting period for this PBRER/PSUR. [redacted] review of the follow-up information did not change the prior assessment of the events of interest; therefore, these cases are not discussed further. Two of the 6 initial cases were from literature and concerned multiple unspecified patients: [redacted] reported the PT Brain injury; and concerned an article which presented the results of an analysis of publications concerning the use of OROS methylphenidate HCl in Brazil for an unspecified number of patients. [redacted] reported the PT Cerebrovascular accident. The study reported in this case involved paediatric and young adult patients and compared the risk for cardiac events in users of OROS methylphenidate HCl and amphetamine salts over a 10 year period. Limited information relating to patient demographics, dosage, latency, details regarding the events and outcome was provided in both of these literature cases, and these cases are not discussed further.

Table 18 displays a count of all PTs from the Cerebrovascular SMQ by age and seriousness in the 4 remaining cases received during the current PBRER/PSUR reporting period (11 October 2012 to 31 October 2013) and cumulatively from the IBD of OROS methylphenidate HCl to the DLP of this report (01 August 2000 to 31 October 2013).

[redacted]

[31] Schelleman H, Bilker WB, Kimmel SE, et al. Methylphenidate and risk of serious cardiovascular events in adults. *Am J Psychiatry* February 2012;169:(2):178-185.

[32] Itaborahy C, Ortega F. Methylphenidate in Brazil: a decade of publications. *Ciencia and Saude Coletiva*, March 2013; 18(3):803-816.

[33] Winterstein AG, Gerhard T, Shuster J, Saidi A. Cardiac safety of methylphenidate versus amphetamine salts in the treatment of ADHD. *Pediatrics*. 2009;124 (1):e75-80.

Table 18: Interim and Cumulative Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Stroke and Cerebrovascular Events

Preferred Term	Number of Events[a,b,c]					
	Interim 11 October 2012 to 31October 2013			Cumulative 01 August 2000 to 31October 2013		
Age (years)	**<18[d]**	**≥18[e]**	**NR[f]**	**<18[d]**	**≥18[e]**	**NR[f]**
Aphasia	-	-	-	3 (1)	2	- (1)
Basal ganglia infarction	-	-	-	2	-	-
Brain hypoxia	-	-	-	1	-	-
Brain injury	-	-	-	-	1	1
Carotid artery disease	-	-	-	-	1	-
Carotid artery dissection	-	-	-	-	1	-
Carotid artery occlusion	-	-	-	1	-	-
Cerebellar infarction	-	-	-	-	1	-
Cerebral artery occlusion	-	-	-	2	-	-
Cerebral artery stenosis	-	-	-	1	-	-
Cerebral haematoma	-	-	-	1	1	-
Cerebral haemorrhage	-	-	-	1	-	-
Cerebral infarction	-	-	-	2	5	-
Cerebral thrombosis	-	-	-	-	1	-
Cerebral vasoconstriction	1	-	-	2	-	
Cerebrovascular accident	-	-	1	3	7	5
Cerebrovascular disorder	-	-	-	1	-	-
Dysarthria	-	-	- (1)	5 (4)	2 (1)	1 (5)
Haemorrhage intracranial	-	-	-	2	1	-
Hemiparesis	-	-	-	3	-	-
Intracranial aneurysm	-	-	-	1	-	-
Intracranial venous sinus thrombosis	-	-	-	1	-	-
Ischaemic cerebral infarction	-	-	-	1	1	-
Ischaemic stroke	-	1	-	1	2	-
Monoplegia	-	-	-	-	1	-
Paralysis	-	-	-	-	1	-
Paresis	-	-	-	1	1	-
Transient ischaemic attack	-	-	-	2	3	-
Vasculitis cerebral	-	-	-	2	-	-
Subtotal	**1**	**1**	**1 (1)**	**39(5)**	**32(1)**	**7(6)**
Total[g]	**4**			**90**		

Key: MPH= Methylphenidate hydrochloride; NR= Not reported, PT= Preferred term

a: Cases may have reported more than 1 event of interest.

b: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified.

c: Dash (-) indicates the specified PT was not identified within the age/age group.

d: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.

e: Includes patients ≥18-years-old and/or patient age category: adult, elderly.

f: Includes patients with no reported age and age category.

g: Includes serious and nonserious events.

An overview of the characteristics of the 4 initial cases included for further review from the current report period (1 patient <18-years-old, 1 patient ≥18-years-old, and 2 patients with no reported age/age category) is presented in Table 19.

Table 19: Characteristics for OROS MPH in Selected Cases Reporting Stroke and Cerebrovascular Events

Characteristics		Number of Cases (n=4)
Sex	Male	3
	Female	1
Age (years)	16	1
	54	1
	Not reported	2
Daily Dose[a]	27 mg	1
	54 mg	1
	72 mg	1
	Not reported	1
Indication	ADHD	1
	Obsessive-compulsive disorder	1
	Not reported	2
Outcome of Event of Interest	Recovered/Resolved	2
	Not reported	2

Key: ADHD=Attention Deficit Hyperactivity Disorder; MPH=Methylphenidate hydrochloride; n=Number of cases
a: Dose at time of event of interest.

Of the 4 cases included for further review, [redacted] reported the PTs Cerebrovascular accident and Dysarthria, respectively, in patients of unspecified age. The cases also provided limited information on medical history, concomitant medications, medication history, latency, and event details. [redacted] OROS methylphenidate HCl for the off label indication of obsessive compulsive disorder also. The patient experienced an Ischaemic stroke, 15 days after the last dose of OROS methylphenidate HCl (he received approximately 7 months of treatment). The patient had no relevant medical history and concomitant medications were not reported. The outcome was not provided.

The remaining case, received from literature, involved a patient <18-years-old and is presented below.

- [redacted] (***Cerebral vasoconstriction***): [redacted] medical history of anxiety and migraine headaches was treated with OROS methylphenidate HCl (dose not reported) for ADHD. Co-suspect medications included sertraline and eletriptan, and concomitant medications included lithium and aripiprazole. On an unspecified date, the patient presented with progressively worsening and constant headaches for 2 weeks. The patient presented twice to the emergency department, describing the pain as throbbing, fronto-temporal and varying in intensity. Magnetic Resonance Imaging (MRI) revealed abnormal fluid-attenuated inversion recovery signal in the left cerebral convexity subarachnoid spaces with scattered sulcal subarachnoid haemorrhage. Computed tomography and computed tomography angiography (CTA) scans revealed multifocal segmental cerebral vasoconstriction involving small-to-medium-sized vessels. A digital subtraction angiography confirmed multifocal segmental vessel narrowing (Call-Fleming

[34] Bain J, Segal D, BS RA, Monoky D, Thompson SJ. Call-Fleming syndrome: headache in a 16-year-old girl. *Pediatr Neurol*. 2013;49(2):130-133.

syndrome). On an unspecified date sertraline and OROS methylphenidate HCl were stopped. The patient was treated with nifedipine and her headaches improved. A repeat CTA 2 months later showed complete resolution of the vasoconstriction (see also Section 16.3.5.2.4, Use in Children).

Discussion

Of the 4 cases identified for further review, [redacted] involving 1 adult patient and 2 patients with unspecified age, provided minimal information, precluding adequate medical assessment. [redacted] diagnosed with Call-Fleming syndrome (a reversible cerebral vasoconstriction syndrome [RCVS]). This disorder is poorly understood but predominantly occurs in female patients; paediatric patients are occasionally seen, though most cases occur in middle-aged patients.[35] Reversible cerebral vasoconstriction syndrome is associated with nonaneurysmal subarachnoid haemorrhage, pregnancy, and exposure to certain vasoactive drugs. Frequently the underlying mechanism of RCVS is mulitfactoral and often the cause in not identifiable.[36] This case is confounded by the use of sertraline, which has been associated with cerebral vasoconstriction syndrome and Call-Fleming syndrome[37] and by eletriptan, for which cerebral haemorrhage, subarachnoid haemorrhage, and stroke have been reported.[38] The patient's headaches resolved completely with appropriate treatment.

Conclusion

The RMP lists cerebrovascular disorders as an important potential risk. Review of these cases does not provide evidence that represent a new safety concern. No changes to the CCDS or RMP are warranted at this time

16.2.1.4. Psychiatric Disorders: Depression and Suicide/Self Injury

Introduction

Suicide, suicide attempt, suicide ideation, self-injurious behaviour, and depression have been identified as events of potential significance with OROS methylphenidate HCl and continue to be presented in PBRER/PSURs.

[35] Reversible Cerebral Vasoconstriction Syndrome. http://www medscape.org/viewarticle/748234_3. Accessed 21 November 2013.

[36] Systematic review of reversible cerebral vasoconstriction syndrome. US National Library of Medicine NIH. http://www ncbi nlm nih.gov/pmc/articles/PMC3020907. Accessed on 01 November 13.

[37] Sertraline. Summary of Product Characteristics. http://www medicines.org.uk/emc/medicine/25805/SPC/Sertraline+100mg+Film+coated+Tablets/#UNDESIRABLE_EFFECTS. Accessed 21 November 2013.

[38] RELPAX® Prescribing Information, Pfizer/Roerig, New York, NY, 10017, http://labeling.pfizer.com/ShowLabeling.aspx?id=621 Accessed on 04 November 2013.

Depression is an RMP identified risk and Suicidality is a potential risk associated with the use of OROS methylphenidate HCl. As part of a commitment detailed in the RMP for OROS methylphenidate HCl, the MAH continues to perform enhanced pharmacovigilance in the form of a targeted questionnaire to reporters of suicidality events.

Suicide, Suicide attempt, and Suicidal ideation are unlisted events in the CCDS. Depression is listed as an ADR in the AE Section of the CCDS.

Methods

A frequency tabulation of MedDRA PTs reported for OROS methylphenidate HCl during the reporting period was reviewed to identify topics for review. The following MedDRA SMQs were selected to identify cases for review: Depression and suicide/self-injury SMQ (Broad). The GMS safety database was then searched to retrieve medically confirmed cases reporting PTs within the SMQ.

Results

The search identified 135 cases (115 initial, 20 follow-up). Of the 135 cases retrieved by the standard search, on further review, 54 cases (see Appendix 7.3) did not report events of depression, suicide, or self-injurious behaviour and are excluded from further review: The majority of these cases (30; see Appendix 7.3) involved PTs Drug abuse, Drug dependence, Intentional drug misuse, or Substance abuse and will be reviewed in Section 16.2.5.1, Drug Abuse/Misuse and 10[39] of the 30 cases will also be reviewed in Section 16.2.5.2, Medication Error. One case (20121010015) reported Intentional overdose without mention of suicide attempt or depression and will be reviewed in Section 16.2.4, Experience with Overdose, Deliberate or Accidental, and its Treatment. Twenty-three of these cases[40] reported PTs Disturbance in attention (7), Initial insomnia (5), Memory impairment (3), Hypersomnia (2), Psychomotor hyperactivity (2), Affect lability (1), Mood altered (1), or Middle insomnia (1) without any additional events suggestive of depression.

Of the remaining 81 cases (67 initial, 14 follow-up), a review of the follow-up cases did not change the prior assessment of the event in 4 cases[41]; these cases are, therefore not discussed further. The remaining 10 follow-up cases[42] contained relevant new information (relevant medical history, relevant concomitant medications, event outcome, new event of interest and medical confirmation) and are included in the review of the initial cases.

[redacted]

Twelve[43] of the remaining 77 cases concerned multiple, unidentifiable patients, with insufficient information (missing dates of therapy, event onset, action taken, medical history, concomitant medications, and outcome) precluding further analysis, and therefore, will not be further discussed.

A detailed case disposition, including total cases identified, and total cases included for analysis is provided in Table 20.

Table 20: Disposition of OROS MPH Cases Involving Depression and/or Suicide/Self-Injury

Cases	Number of Cases	
	Initial	Follow-Up
Total Number of Reported Cases	**115**	**20**
Total Cases Not Further Evaluated	**60**	**10**
No reported event of depression and/or suicide/self-injury	48	6
Follow-up cases with no significant new information	N/A	4
Multiple patient cases with no patient identifiers	12	0
Total Included Cases for Analysis	**55**	**10**

Key: MPH=Methylphenidate hydrochloride; N/A=Not applicable

Table 21 displays a count of the selected PTs by age and seriousness for the remaining 65 cases (55 initial, 10 follow-up) included in the current PBRER/PSUR reporting period.

[redacted]

Table 21: Interim Count of Selected PTs by Seriousness in Cases With OROS MPH: Depression and Suicide/Self Injury

Preferred Term	Number of Events[a,b]		
Age (years)	**< 18[c]**	**≥ 18[d]**	**NR[e]**
Anhedonia	(1)	-	-
Apathy	(1)	-(1)	-
Blunted affect	(1)	-	-
Completed suicide	1	1	-
Crying	(5)	-(1)	-
Depressed mood	(5)	-(2)	-(1)
Depression	14(3)	7(1)	1
Depression suicidal	-	-	1
Drug abuse	-	-	1
Drug dependence	-	-	1
Dysphoria	(2)	-(2)	-(1)
Intentional overdose	4	7	-
Major depression	-	-	1
Mood altered	2	-	-
Mood swings	(1)	-	-
Poisoning deliberate	(1)	-	-
Self injurious behaviour	1	-	-
Suicidal ideation	6	1	-
Suicide attempt	10	7	-
Tearfulness	(3)	-	-
Subtotal	**39(23)**	**23(7)**	**5(2)**
Total[f]	**62**	**30**	**7**

Key: MPH=Methylphenidate hydrochloride, NR=Not reported, PT=Preferred term
a: Cases may have reported more than 1 event of interest.
b: Events reported from medically confirmed cases
c: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
d: Includes patients ≥18-years-old and/or patient age category: adult, elderly.
e: Includes patients with no reported age and age category.
f: Includes serious and nonserious events.
g: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified.
h: Dash (-) indicates the specified PT was not identified within the age/age group.

Twenty-nine cases (see Appendix 7.3) reported listed events of interest, including Depression (19), Depressed mood (7), Tearfulness (3), Major depression (1), Mood altered (1), and Mood swings (1). Five[44] of the 29 cases also reported the following unlisted events related to depression: Crying, Apathy, or Dysphoria. [redacted] included events of drug dependence, drug abuse, or drug diversion and will be reviewed in Section 16.2.5, Drug Abuse/Misuse. [redacted] will also be reviewed in Section 16.2.5.2, Medication Error.

For the remaining 36 cases (see Appendix 7.3 for AER numbers), [22 patients <18-years-old, 12 patients ≥18-years-old, and 2 patients with no reported age/age category]), an overview of the characteristics of the 22 cases in <18-year-old patients and 12 cases in ≥18–year-old patients is presented in Table 22 and Table 23 respectively. [redacted] with no reported age/age category reported 2 patients of unknown

[44] 20121102326, 20130111546, 20130309985, 20130513098, 20131013138

sex. One of these patients from the United Kingdom received an unspecified dose for ADHD and experienced low emotional state, irritability, and dysphoria at the end of the day when OROS methylphenidate HCl was wearing off. Outcome of the events were not reported. The other patient from Sweden received 54 mg of OROS methylphenidate HCl instead of 18 mg and experienced depressive suicidal thoughts 3 days later. The action taken with OROS methylphenidate HCl was not reported and the patient recovered (see also Section 16.2.5.2, Medication error/Maladministration).

Table 22: Characteristics for OROS MPH Cases Reporting Depression and/or Suicide/Self-Injury in Patients <18-Years-old

Characteristic		Number of Cases (n=22)
Source	Spontaneous	20
	Literature	2
Patient Sex	Male	12
	Female	10
Patient Age (Years)	≤5	0
	6-12	7
Mean: 12.7	13-17	13
Median: 13	Child	2
Daily Dose at Onset of Adverse Event	18 mg	2
	27 mg	4
	36 mg	4
	45 mg	1
	54 mg	4
	162 mg	1
	720 mg	1
	810 mg	1
	1134 mg	1
	1620 mg	1
	Not reported	2
Latency	1 week to 1 month	2
	>1 month to 6 months	2
	> 6 months to 1 year	0
	>1 year	4
	Not reported	14
Event Outcome	Recovered	12
	Not recovered	3
	Fatal	1
	Recovering	1
	Not reported	5
Relevant Medical History[a]	Depression	1
	Previous suicide attempt	2
	Conduct disorder	1
	Unspecified psychosocial stressors	1
	Emotional distress	1
	Emotional issues and crying while taking lisdexamfetamine	1
	Oppositional defiant disorder	1
	Sexual abuse	1
	Substance use disorder	1
	Spina bifida	1

Table 22: Characteristics for OROS MPH Cases Reporting Depression and/or Suicide/Self-Injury in Patients <18-Years-old

Characteristic		Number of Cases (n=22)
	Narcolepsy	1
Country of Origin	Germany	4
	United Kingdom	4
	Turkey	3
	United States	3
	Israel	1
	Norway	2
	Australia	1
	Canada	1
	Denmark	1
	France	1
	South Africa	1

Key: MPH=Methylphenidate hydrochloride; n=Number
a: One case may report more than 1 relevant medical history.

Table 23: Characteristics for OROS MPH Cases Reporting Depression and/or Suicide/Self-Injury in Patients ≥18-Years-old

Characteristic		Number of Cases (n=12)
Source	Spontaneous	10
	Literature	2
Patient Sex	Male	5
	Female	7
Patient Age (Years)	≥ 18 to 30	5
	≥31 to 50	4
Mean: 37	≥51 to 65	2
Median: 38.5	Adult	1
Daily Dose at Onset of Adverse Event	18 mg	1
	36 mg	1
	140 mg	1
	540 mg	2
	720 mg	1
	1512 mg	1
	Not reported	5
Latency	Not reported	12
Event Outcome	Recovered	4
	Fatal	3
	Not reported	5
Relevant Medical History[a]	Suicide ideation	1
	Depression	1
	Previous suicide attempt	3
	Bipolar psychosis due to marijuana withdrawal	1
	Psychosocial stressor	1
	Substance use disorder	1
	Personality disorder	2
	Social phobia	1
	Mood disorder	1

Table 23: Characteristics for OROS MPH Cases Reporting Depression and/or Suicide/Self-Injury in Patients ≥18-Years-old

Characteristic		Number of Cases (n=12)
Country of Origin	Germany	7
	United States	3
	Austria	1
	Iceland	1

Key: MPH=Methylphenidate hydrochloride; n=Number
a: One case may report more than 1 medical history.

All 36 cases were medically reviewed. [redacted] with no reported age/age category were previously described. Six non-serious cases[45] reported the following events of interest: Dysphoria (2 cases), and 1 case each of Anhedonia, Apathy, Blunted affect, Crying, and Disturbance in attention.

For the remaining 28 serious cases, 5 cases[46] provided insufficient information regarding latency, medical history, concomitant medications, action taken with OROS methylphenidate HCl, and/or outcome precluding further assessment.

Eleven cases described an intentional overdose with OROS methylphenidate HCl and/or multiple drugs in a suicide attempt. It was not reported if OROS methylphenidate HCl was routinely prescribed for 7 of these patients.[47] [redacted] the patient was not prescribed OROS methylphenidate HCl and [redacted] did not report the brand of methylphenidate that was used. [redacted] it was not clear if the patient was being treated with OROS methylphenidate HCl at the time of the event. [redacted] was also confounded by a history of a prior suicide attempt after [redacted] father died and feelings of guilt after a recent robbery attempt.

In 3 cases, treatment with OROS methylphenidate HCl continued after the patient attempted to commit suicide and the patient recovered. [redacted] with oppositional defiant disorder who attempted to commit suicide following an argument with his brother approximately 1 year after initiation of OROS methylphenidate HCl 36 mg. The patient did not take his medication the day of the attempted suicide. Treatment with OROS methylphenidate HCl continued (dose was not changed) and the patient recovered. The [redacted] with a history of a previous suicide attempt, emotional distress, personality disorder, morbid thoughts, and alcohol abuse receiving OROS methylphenidate HCl "140 mg" for personality disorder (an unapproved indication). The patient attempted to commit suicide by taking OROS methylphenidate HCl 108 mg and methylphenidate 20 mg, fluoxetine 100 mg, prothipendyl 160 mg, tetrazepam 100 mg and ethanol (9 bottles). Treatment with OROS methylphenidate HCl continued (dose was not changed) and the patient recovered. [redacted]

- [redacted]
- [redacted]
- [redacted]

with a history of depression and previous suicide attempt who attempted to commit suicide by taking OROS methylphenidate HCl 594 mg and ethanol (intentional drug overdose) at an unspecified time after initiation of OROS methylphenidate HCl. On the same day, he experienced tachycardia (150 to <160 bpm), extrapyramidal symptoms, agitation, and was "slowed". Treatment with OROS methylphenidate HCl continued (dose was not changed) and the patient recovered.

The 9 remaining serious cases (8 patients < 18-years-old, and 1 patient ≥ 18-years-old) are presented in Table 24.

Table 24: Selected Serious OROS MPH Cases Reporting Depression and Suicide/Self injury

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d] Concomitant Medications	Medical History	Comments
Patients < 18-years-old					
Patients 6 to 12 years old					
[redacted] Canada [redacted]	ADHD 36 mg 28 days	**Suicidal ideation**	*Methylphenidate/* NR	NR	The patient experienced suicidal thoughts 24 days after initiation of OROS MPH 18 mg and 7 days after the dose was increased to 36 mg. The patient was also receiving (non-Company) MPH 20 mg. On an unspecified date the dose of OROS MPH was decreased to 27 mg and the dose of MPH was decreased to 10 mg. Treatment with OROS MPH continued and the action taken with MPH was not reported. The patient had not recovered (see also Section 16.3.5.2.4, Use in Children). *Follow-up information was received from a health care professional and the case is now medically confirmed.*
[redacted] United Kingdom [redacted]	ADHD 27 mg 13.5 months	**Completed suicide**	*NR/* Melatonin MPH	Emotional distress Sexual abuse Sleep disorder	The patient's dose of OROS MPH was increased from 18 to 27 mg approximately 2 months prior to the event. [redacted] seen by her physicdian a few months before the event and showed no signs of suicidal tendencies. However, the patient had possibly been subjected to sexual abuse in the past and was being neglected at the time of her death. [redacted] hanging in her room and died shortly after despite cardiopulmonary resuscitation. An autopsy revealed the cause of death as suspension by the neck and pressure around the neck (see also Section 16.3.5.2.4, Use in Children). *Follow-up information received included new medically relevant medical history and that the reporter was unsure if suicide was the actual intention as there was no note left.*

Table 24: Selected Serious OROS MPH Cases Reporting Depression and Suicide/Self injury

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d] Concomitant Medications	Medical History	Comments
[redacted] Denmark [redacted]	ADHD 54 mg 57 days	**Suicide attempt** **Depression** **Suicidal ideation** **Depressed mood** **Social avoidant behaviour**	*NR/* Fluoxetine Medikinet (MPH) Ritalin (MPH)	Suicide attempt Asperger's disorder	The patient experienced depression 57 days after initiation of OROS MPH. The month before the patient was feeling sad and socially withdrawn. Treatment with (non-Company) MPH was initiated 2 months after OROS MPH. The patient was diagnosed with severe depression and hospitalized. OROS MPH and MPH were discontinued. A second non-Company MPH was started. On an unspecified date the patient developed suicidal thoughts. The patient had experienced a prior suicide attempt. The second MPH was discontinued. The patient recovered from the depression and the outcome for suicidal ideation and suicide attempt was not reported (see also Section 16.3.5.2.4, Use in Children).
[redacted] Australia [redacted]	ADHD 27 mg NR	**Suicidal ideation** **Depression**	*NR/* NR	NR	The patient was taking (non-Company) immediate release MPH and was switched to OROS MPH 27 mg. On an unspecified date the patient became depressed and suicidal. OROS MPH was discontinued and the patient was switched back to MPH and was doing well. The patient recovered from the events (see also Section 16.3.5.2.4, Use in Children).

Table 24: Selected Serious OROS MPH Cases Reporting Depression and Suicide/Self injury

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d] Concomitant Medications	Medical History	Comments
Patients 13 to 17 years-old					
[redacted] Turkey [redacted]	ADHD 27 mg NR	**Suicide attempt** **Depression** **Abnormal behaviour** Overdose Nausea Vomiting Palpitations	*Sertraline* *Ritalin /* Risperidone	Depression Cardio-respiratory arrest Affective disorder Conduct disorder Oppositional defiant disorder The patient's mother had a history of panic attacks and was followed up by psychiatry	The dose of OROS MPH was increased from 27 mg to 36 mg and risperidone was added for conduct disorder. The patient subsequently experienced depressive symptoms and was treated with sertraline. One month later, risperidone was withdrawn. The patient attempted suicide with OROS MPH (2 boxes) 1 month after risperidone withdrawal and 4 months after initiation of OROS MPH 27 mg. He wrote a suicide note stating that the reason for the suicide attempt was that his family mistreated him. The patient did not take his medications regularly prior to the suicide attempt and had depressive symptoms. He was hospitalised the same day due to foaming from the mouth and behavioural problems. Non-Company MPH and risperidone were administered because OROS MPH "was not prescribed". Risperidone was withdrawn. The action taken with sertraline was not reported. OROS MPH was stopped for 1 month and then restarted 6 months later at 36 mg daily. The patient recovered from signs of risky behaviour, depression, and suicide attempt (see also Section 16.3.5.2.4, Use in Children). *Follow-up information received included relevant medical history, concomitant medications (risperidone was previously reported as suspect), action taken with OROS MPH, and outcome of the events.*

Table 24: Selected Serious OROS MPH Cases Reporting Depression and Suicide/Self injury

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d] Concomitant Medications	Medical History	Comments
[redacted] Turkey [redacted] Literature	ADHD 54 mg Approximately 3 years	**Suicide attempt** **Intentional overdose** Treatment noncompliance Sinus tachycardia	*NR/* NR	Substance use disorder	The patient was treated with OROS MPH since age 11. The patient impulsively decided to commit suicide after an argument with his girlfriend by taking 60 OROS MPH 54 mg (3240 mg) tablets. Approximately 2 hours later the patient experienced palpitations and sinus tachycardia. The patient was treated with active charcoal and recovered from the suicide attempt. It was reported that the patient discontinued his medication on his own 3 months prior to the event (see also Section 16.3.5.2.4, use in Children).
[redacted] United States [redacted]	ADHD 27 mg 13 days	**Suicidal ideation** **Depression**	*Lisdexamfetamine /* Blinded study vaccine	Constipation Encopresis Spina bifida occulta	The patient experienced suicidal ideation 13 days after initiation of OROS MPH 27 mg. The patient had previously been treated with lisdexamfetamine dimesylate and was switched to OROS MPH due to increased emotion and not focusing. The patient was also receiving blinded study vaccine in a clinical study. The patient was admitted to a psychiatry unit for suicidal ideation and depression. OROS MPH was discontinued and the patient was treated with sertraline. The patient recovered from the suicidal ideation and was recovering from depression (see also Section 16.3.5.2.4, Use in Children).
[redacted] Norway [redacted]	Narcolepsy 54 mg Approximately 2 years	Dependent personality disorder **Suicidal ideation** **Depression** Aggression Off label use	*NR/* Clomipramine Omeprazole	Narcolepsy in connection with Streptococcal infection	The patient experienced aggression, depression, suicidal thoughts, and hostility toward her family approximately 2 years after initiation of OROS MPH. The patient stopped doing her homework and exhibited passive and self-injurious behaviour that increased over the past 2-4 weeks. The patient was hospitalised. OROS MPH was discontinued and the patient had not recovered (see also Section 16.3.5.2.4, Use in Children).

Table 24: Selected Serious OROS MPH Cases Reporting Depression and Suicide/Self injury

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d] Concomitant Medications	Medical History	Comments
Patients ≥ 18-years-old					
[redacted] Turkey [redacted] Spontaneous	Social phobia 36 mg NR	**Suicide attempt** **Intentional overdose** Off label use	*Sertraline/* NR	Social phobia	The patient attempted suicide by taking 13 OROS MPH 36 mg tablets and 4 sertraline tablets. It was not reported if sertraline was prescribed. The patient was hospitalised and discharged the next day. Action taken with OROS MPH was not reported. The patient recovered from the suicide attempt.

Key: AER#= Adverse event report number; ADHD= Attention Deficient Hyperactivity Disorder; MedDRA= Medical Dictionary for Regulatory Activities; MPH= Methylphenidate hydrochloride; NR= Not reported, PT= Preferred term

a: Daily dose at the time of the event of interest.
b: Time from the first exposure to OROS MPH to onset of event of interest.
c: Events of interest are in **bold**.
d: Co-suspect medications are *italicised.*
e: Kilicoglu AG, Ipek H, Mutlu C, et.al. Methylphenidate for suicide attempt.

Discussion

ADHD patients are subject to inherent background risks for suicidal behaviour. In the US, the annual rate of completed suicide for those aged 10 to 19 years was 4.6 per 100,000 persons.[48] A review of the literature by James et al, determined that the rate of completed suicide in males (aged 5 to 24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population.[49] In another literature article regarding clinical risk factors seen in patients who have completed suicide, more than 90% of those who complete suicide have a diagnosable psychiatric illness at the time of death, usually depression, alcohol or substance abuse, or both.[50]

A total of 81 cases suggestive of depression and suicide/self injury were reported during the current PBRER/PSUR period, and 65 were included for further analysis. Of these, 9 were identified for further review; 8 concerned patients who were <18-years-old (4 patients 6 to 12-years-old and 4 patients who were 13 to 17-years-old), and 1 concerned a patient ≥18-years-old.

Patients <18-years-old

Six[51] of the 8 cases provided relevant medical history or comorbid condition (ie, depression, previous suicide attempts, emotional distress, sexual abuse, substance use disorder, and narcolepsy that confounded assessment of a drug-event association. A wide range of mental disorders increase the odds of experiencing suicidal ideation.[52] Suicide rates among young people have been increasing to such an extent that they are now the highest risk group in a third of countries.[53]

In another [redacted] the patient was receiving both OROS methylphenidate HCl and non-Company methylphenidate and experienced suicidal thoughts after the dose of OROS methylphenidate HCl was increased to 36 mg. Both OROS methylphenidate HCl and methylphenidate doses were decreased and the patient had not recovered at the time of the event.

[redacted] who experienced depression and suicidal thoughts after switching from non-Company methylphenidate immediate release to OROS methylphenidate HCl. Treatment with OROS methylphenidate HCl was discontinued.

[48] Miniño AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: Final data for 2000. National Vital Statistics Reports, 50(15). Hyattsville, MD: National Center for Health Statistics, 2002.

[49] James A, Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: A review of possible associations. *Acta Psychiatr Scand*. 2004(110): 408-415.

[50] Gaynes BN, West SL, Ford CA, Fram P, Klien J, Lohr KN. Screening for suicide risk in adults: A summary of the evidence for the U.S. Preventative Services Task Force. *Ann Internal Med*. 2004;140(10):822—837.

[51] [redacted]

[52] Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, et al. (2009) Cross-National Analysis of the Associations among Mental Disorders and Suicidal Behavior: Findings from the WHO World Mental Health Surveys. PLoS Med 6(8): e1000123.

[53] Suicide. World Health Organisation. http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/. Accessed on 30 October 2012.

The patient restarted non-Company methylphenidate and patient recovered. Although there is a positive dechallenge with OROS methylphenidate HCl, the lack of information regarding latency, medical history, and concomitant medications precludes further assessment.

Patients ≥18-years-old

[redacted] with social phobia attempted suicide by taking 13 OROS methylphenidate HCl 36 mg tablets and 4 sertraline tablets. No details regarding onset latency, concomitant medication or action taken with OROS methylphenidate HCl were provided to allow for adequate medical assessment of this case.

Conclusion

Review of the cases in this reporting period did not identify any patterns or new safety information with respect to depression, suicide, and self-injurious behaviour and related events. No changes to the CCDS or RMP are warranted at this time.

16.2.2. Efficacy-Related Information

Introduction

Cases associated with lack of efficacy are reviewed in all PBRER/PSURs. The CCDS states that as the effect of OROS methylphenidate HCl "*has been shown to be present 12 hours after dosing, the product should be taken once daily in the morning*".

Methods

The GMS safety database was searched for all cases involving OROS methylphenidate HCl received during this reporting period that met PBRER/PSUR reporting criteria and were coded to MedDRA PTs in the standardised MedDRA Query for Lack of Efficacy/Effect (see Appendix 7.1).

Results/Discussion

A total of 143 medically confirmed cases (133 initial, 10 follow-up) reporting a lack of efficacy were received during the reporting period (see Appendix 7.3 for AER numbers). A review of the follow-up information did not change the prior assessment of this topic in all 10 cases,[54] these cases are, therefore, not discussed further.

Of the 133 initial cases, 10 literature cases[55] concerned multiple, unidentifiable patients (See Appendix 7.4 for list of references). Of these, the following PTs were reported: Drug ineffective (7), and 1 each of Drug effect decreased, Drug tolerance, and Therapeutic response decreased. Six of the cases involved paediatric patients: in [redacted] there were 90 patients involved in the trial which studied the statistical difference between responders and

[redacted]

[redacted]

non-responders; [redacted] concerned a study to document changes in liver functions tests associated with risperidone use and also involved an unknown number of patients treated with OROS methylphenidate HCl; [redacted] involved 97 paediatric patients treated with OROS methylphenidate HCl 18 to 54 mg/day in a 1 year follow-up trial. It was reported that 4 of the patients experienced treatment failure and discontinued from the study; [redacted] concerned the most commonly reported AEs in paediatric patients. Of 3,755 reports of methylphenidate use, lack of drug effect was one of the 5 most reported AEs; [redacted] a study of 1,098 paediatric patients or which 167 left the trial due to lack of effect, AEs, lack of compliance and other reasons; [redacted] involved an unreported number of patients involved in a study in which efficacy was assessed. The dosage was adjusted if an acceptable response was not achieved. Of the 3 cases involving adult patients, [redacted] concerned a study in which efficacy was determined in 8 patients with cocaine dependence treated with 54 mg OROS methylphenidate HCl; [redacted] concerned 116 patients who answered a questionnaire stating if they had received treatment with methylphenidate. An unspecified number of patients experienced lack of efficacy. [redacted] reported drug tolerance syndrome in an unspecified amount of patients, requiring an increase in dosage. The remaining literature [redacted] involving multiple patients did not specify the age groups, and no information was reported regarding the subtherapeutic response. In all these cases, limited information relating to patient demographics, dosage, latency, details regarding the event and outcome were provided precluding adequate medical assessment.

This is also the case for 11 spontaneous cases,[56] received from physicians or nurses, which also concerned multiple, unidentifiable patients. The following PTS were reported in these 11 cases: Drug ineffective (7), Drug effect decreased (2), and Therapeutic response decreased (2). Of these, 3 cases involved paediatric patients: [redacted] stated that OROS methylphenidate HCl did not work as well in some ADD children; [redacted] concerned multiple patients who experienced insufficient duration of drug effect and it was queried by the physician if the duration was 6 to 7 hours; [redacted] concerned a "couple" of paediatric patients in which medication was not working compared to non-Company methylphenidate. [redacted]) involved adult patients, and involved a lack of effect reported by a nurse in an unspecified amount of patients. There were 7 cases in which the age group of the multiple patients was not specified: case 20121103610 reported an increase in dosage due to lack of efficacy by a pharmacist for an unknown number of patients; 2 cases [redacted]) concerned multiple patients who experienced lack of effect; [redacted] reported lack of drug effect when patients were switched from non-Company OROS methylphenidate HCl to Company drug. The patients were switched back again but decreased drug effect persisted; in [redacted] the physician stated that there were "a few cases whereby medication effect was wearing off after 8 hours, i.e. by 2 to 3 pm"; [redacted] reported that the efficacy was not verified during the 12 hours and therapeutic response was decreased in an unspecified number of patients, and [redacted] reported that the patient's parents informed the physician that OROS methylphenidate HCl was not

[redacted]

working compared to non-Company methylphenidate. The cases provided very limited information and are also not discussed further.

Table 25 displays a count of the selected PTs by age and seriousness in the remaining 112 cases received for the current PBRER/PSUR reporting period.

Table 25: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Lack of Efficacy

Preferred Term	Number of Events[a,b]		
Age (years)	**<18[c]**	**≥18[d]**	**NR[e]**
Drug effect decreased	- (8)	1 (4)	- (6)
Drug effect incomplete	- (2)	-	- (1)
Drug ineffective	1 (33)	0 (26)	- (12)
Therapeutic response decreased	- (8)	- (4)	-
Therapeutic response delayed	- (1)	- (2)	- (1)
Drug level decreased	-	- (2)	-
Subtotal	**1(52)**	**1 (38)**	**0 (20)**
Total[f]	**112**		

Key: MPH=Methylphenidate hydrochloride; NR=Not reported, PT=Preferred term
a: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified.
b: Dash (-) indicates the specified PT was not identified within the age/age group
c: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
d: Includes patients ≥18-years-old and/or patient age category: adult, elderly.
e: Includes patients with no reported age and age category.
f: Includes serious and nonserious cases.

In 107 of the 112 cases identified for further review, the lack of efficacy event was nonserious and listed in the CCDS for OROS methylphenidate HCl. The following PTs were reported: Drug ineffective (71), Drug effect decreased (18), Therapeutic response decreased (12), and Drug effect incomplete (3), and Therapeutic response delayed (3). These cases are not discussed further.

There were 3 nonserious cases in which the lack of efficacy event was unlisted; Drug level decreased (2) and Therapeutic response delayed (1). In the 2 cases of Drug level decreased ([redacted] both involving adults, symptoms were not reported and the dose of OROS methylphenidate HCl was not changed ([redacted] the patient had felt better since taking OROS methylphenidate HCl). In the case of Therapeutic response delayed [redacted], it was noted that the effect of OROS methylphenidate HCl was not seen until about 1 hour after the medication was taken by the patient (age not specified); the dose was not changed.

The remaining 2 cases are discussed below.

Patients <18-years-old

- [redacted] **(Suicidal ideation, *Drug ineffective*):** [redacted] his second decade presented with behavioural and attention difficulties, symptoms which had been present from an early age. The patient was diagnosed with ADHD and had been on trials of both OROS methylphenidate HCl and co-suspect drug amphetamine/dextroamphetamine. Concomitant medications were not reported. On an unspecified date, while on OROS methylphenidate HCl, the patient developed suicidal ideations and would get very irritated. Treatment with amphetamine/dextroamphetamine and OROS methylphenidate HCl was withdrawn and the patient was treated with dexmethylphenidate, which was well tolerated and titrated up to 20 mg over 8 months. Later an additional 5 mg of methylphenidate HCl was administered in response to residual symptoms of ADHD. On an unspecified date, [redacted], the patient had an abrupt onset of neurological symptoms and was hospitalised. He was discharged and 1 month later returned to hospital complaining of persistent headache, short term memory loss, and ataxia. An electroencephalogram demonstrated episodic slowing without epileptiform discharges. An adrenocorticotropic hormone stimulation test identified adrenal insufficiency, so the patient was discharged home on hydrocortisone. The patient was continuing treatment with dexmethylphenidate at the time of the report. The outcome of suicidal ideations and lack of efficacy was not reported. Both events were considered to be possibly related to OROS methylphenidate HCl (see Section 16.2.1.4, Depression and Suicide/Self-injury, and Section 16.3.5.2.4, Use in Children).

Patients ≥18-years-old

- [redacted] **(Depression, *Drug effect decreased*, Fatigue):** A[redacted] age was treated with OROS methylphenidate HCl for an unspecified indication. Concomitant medications were not reported. On an unspecified date, it was reported that when the effects of OROS methylphenidate HCl wore off, the patient felt fatigued and very depressed, and he refused to continue treatment any longer. The events of depression, fatigue, and drug effect decreased were considered possibly related to OROS methylphenidate HCl by the reporter and the outcome was not reported. No further information was available, precluding adequate medical assessment.

The Council for International Organisations of Medical Sciences (CIOMS) Working Group V notes that no drug is adequately effective in all patients treated, and that it is expected that there be a proportion of non-responders for any medical therapy.[58]

Conclusion

Based on this review, no changes to the CCDS are warranted at this time.

[57] Cosme Cruz RM, Clark CM, Shin L. A 10 year-old boy with ADHD Symptoms. *Pediatric Annals*. 2012;41 (11):456-458.

[58] Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V, 121 (Geneva 2001).

16.2.3. Drug Interactions

Introduction

According to the CCDS Section Interactions: *"CONCERTA should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitor (see Contraindications). Because of possible increases in blood pressure, CONCERTA should be used cautiously with vasopressor agents. Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate."* The RMP also lists possible and identified interactions with the following: alcohol, halogenated anaesthetics, centrally acting alpha-2 agonists (eg, clonidine), and dopaminergic drugs.

Methods

The GMS safety database was searched for medically [redacted]

[redacted] nitial, 3 follow-up) reporting a drug interaction were received during the reporting period. A review of the follow-up cases did not change the prior assessment of the event in 2 cases ([redacted]); these cases are, therefore, not discussed further. The remaining follow-up case ([redacted] upgraded the event to serious and is therefore included in the analysis of the initial cases. One initial literature case ([redacted]) concerned multiple unidentifiable patients who received OROS methylphenidate HCl for ADHD and experienced various events including medication intolerance (Drug intolerance) without further suggestion of a drug interaction. This case is not further discussed.

Of the remaining 8 cases, 3 patients were <18-years-old, 4 patients were ≥18-years-old, and age/age category was not reported for 1 patient. All 8 cases are presented in Table 26 below.

[redacted]

[60] Wikström G. Livshotande hjartsvikt av ADHD-medicinering Life-threatening heart failure from ADHD-medication in Lakartidningen. *Lakartidningen* 2012;109 (45):2016-2018.

[61] Mendonca de Andrade CR, Parreiras da Silva WA, Ferreira Belizario Filho J, Cavalheiro da Silveira JC. Attention deficit hyperactivity disorder (ADHD). *Rev Med Minas Gerais* 2011; 21/4:455-464.

Table 26: OROS MPH Select Cases Reporting Drug Interaction

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d]/ Concomitant Medications	Medical History	Comments
Patients <18-years-old					
[redacted] France [redacted] Spontaneous	ADHD 18 mg NR	Dysphemia Abnormal behaviour Tic **Drug interaction** Therapeutic response decreased	*Risperidone/* NR	Educational difficulties (in foster care since age of 2 years)	On an unspecified date, the therapeutic effect was observed to be normal in the morning (reduced agitation) but relapsed in the afternoon despite dosage of OROS MPH increase to 36 mg/day. Reduction of effect was observed at 10 mg/day on a later date and the dose increased to 54 mg/day. When the patient subsequently started at secondary school, his behavioural difficulties again worsened. Risperidone was introduced and an unspecified time later, tics and stutter were observed and agitation persisted. OROS MPH was discontinued and risperidone was continued. Tics and stutter resolved completely an unspecified time later. Bipolar disorder was suspected. Outcome of the events drug interaction, worsening of behavioural problems, and therapeutic effect decreased was not reported.
[redacted] United Kingdom [redacted] Spontaneous	NR NR NR	**Drug interaction** Drug effect decreased	*Carbamazepine/* NR	NR	The patient experienced significantly reduced efficacy of OROS MPH on an unspecified date. Action taken and outcome were not reported. The reporter suspected a possible drug interaction between OROS MPH and carbamazepine resulting in a reduced drug effect of OROS MPH.
[redacted] Japan [redacted] Spontaneous	NR NR NR	Drug effect decreased **Drug interaction**	*Fexofenadine* *Epinastine/* NR	NR	The patient experienced decreased efficacy of OROS MPH on an unspecified date. The reporter stated that the decreased efficacy was presumably associated with "emotional matters". Action was not reported, but the patient's condition returned to the level experienced prior to exposure to the 2 co-suspect medications. The reporter suspected a possible drug interaction between OROS MPH and fexofenadine and epinastine.
Patients ≥18-years-old					
[redacted] Denmark [redacted]	ADHD 36 mg 20 months	Swelling Arthralgia **Drug interaction**	*Methylphenidate* *Ethanol/* NR	NR	Co-suspect drugs were an unspecified MPH product (10 mg) which was commenced approximately 7 months prior to OROS MPH, and ethanol. The patient experienced joint pain and swelling, which increased when she drank red wine. A general physician could not confirm active arthritis. Action taken concerning OROS MPH and unspecified methylphenidate was not reported. An interaction between OROS MPH, unspecified MPH, and red wine was suspected. Outcome was not reported.

Table 26: OROS MPH Select Cases Reporting Drug Interaction

AER# Country Age (years)/Sex Source	Indication Daily Dose[a] Latency[b]	Adverse events (MedDRA PTs)[c]	*Co-suspect*[d]/ Concomitant Medications	Medical History	Comments
[redacted] Germany [redacted] Spontaneou[redacted]	NR NR NR	Syncope **Drug interaction**	*Ethanol*/ NR	NR	The patient was treated with a single dose of sustained release OROS MPH. It was not known if she had received the drug before, or how often. She experienced syncope and was taken to a poison control centre, where blood alcohol level was seen to be 1.5 per thousand (unit not specified) 5.5 hours after exposure to OROS MPH. Symptoms (unspecified) were reported as moderate. Action taken and outcome were not reported. A drug interaction between OROS MPH and ethanol was suspected.
[redacted] Denmark [redacted] Spontaneou[redacted]	ADHD 54 mg 3 months	Delusion **Drug interaction**	*Ethanol*/ NR	NR	The patient drank 5 beers (quantity not further specified) 1 evening and reported to the police that she had been raped by 2 men. Four days later she became aware that this was, in fact, a delusion of being raped. It was considered that she had recovered. Laboratory values on an unspecified date for electrocardiogram, liver function test, fluids and thyroid stimulating hormone were normal. OROS MPH was discontinued by her physician a few days later. A drug interaction between OROS MPH and ethanol was suspected.
[redacted] Switzerland [redacted] Spontaneous	NR 72 mg NR	**Food interaction** Therapeutic response decreased	*NR*/ NR	NR	On an unspecified date, the patient suspected decreased efficacy of OROS MPH after she drank a lot of milky coffee. After reducing her milky coffee consumption, she reported good efficacy of her medication. A drug-food interaction was suspected.
Patients With No Reported Age/Age Category					
[redacted] United Kingdom NR/Male Spontaneous	NR NR NR	Depression **Drug interaction**	*Antidepressants*/ NR	NR	The patient took OROS MPH and subsequently experienced depression on an unspecified date. Action taken and outcome were not reported. A drug interaction between OROS MPH and unspecified antidepressants was suspected.

Key: AER#=Adverse event report number; ADHD=Attention Deficit Hyperactivity Disorder; MedDRA=Medical Dictionary for Regulatory Activities; NR=Not reported, PT=Preferred term

a: Daily dose at the time of the event of interest.
b: Time from the first exposure to OROS methylphenidate HCl to onset of event of interest.
c: Events of interest are in **bold**.
d: Co-suspect medications are *italicised.*
e: Follow-up case.

Discussion

There were no cases identified that reported a drug interaction between OROS methylphenidate HCl and clonidine.

Patients <18-years-old

[redacted] with ADHD experienced tics and stutter after starting treatment with risperidone and following decreased therapeutic response with OROS methylphenidate HCl. OROS methylphenidate HCl was discontinued and risperidone was continued. The tics and stutter resolved completely an unspecified time later. Motor and verbal tics and psychotic or manic symptoms are listed events in the CCDS for OROS methylphenidate HCl. The events in this patient may be associated with an increase in the dose to 54 mg, which is the maximum recommended dose in children. The SmPC for risperidone states that the combined use of psychostimulants (e.g., methylphenidate) with risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.[62] The CCDS for OROS methylphenidate HCl does not report any interactions with antipsychotics.

Of the 2 remaining cases involving patients <18 years of age, both reported lack of effect (LOE) following the suspected drug interaction. [redacted] reported a suspected drug interaction with OROS methylphenidate HCl and carbamazepine in an 8-year-old male who experienced significantly reduced efficacy of OROS methylphenidate HCl. Action taken and outcome were not reported. The CCDS for OROS methylphenidate HCl states that the metabolism of anticonvulsants may be inhibited, but does not specifically mention carbamazepine or any possible effect of such an interaction on OROS methylphenidate HCl. The lack of information relating to therapy start dates, dose, latency, event, or outcome precludes further assessment. In the remaining [redacted]), a child (age and sex not reported) reported decreased efficacy of OROS methylphenidate HCl ("emotional matters") on an unspecified date following a possible drug interaction with fexofenadine and epinastine. Action taken was not reported, but the patient's condition returned to the level experienced prior to exposure to the 2 co-suspect medications. The SmPC for fexofenadine states that this drug does not undergo hepatic biotransformation and therefore will not interact with other medicinal products through hepatic mechanisms. Furthermore, the psychiatric events of insomnia, nervousness, and sleep disorders are listed events.[63] Lack of details regarding this patient's symptoms and medical history precludes further analysis.

[62] Risperidone. Electronic Medicines Compendium. http://www medicines.org.uk/emc/medicine/12818/SPC/Risperdal+Tablets%2c+Liquid+%26+Quicklet/. Accessed 26 November 2013.

[63] Fexofenadine. Electronic Medicines Compendium. http://www medicines.org.uk/emc/medicine/6659/SPC/Telfast+120mg+film-coated+tablets/. Accessed 26 November 2013.

Patients ≥18-years-old

Three cases reported an interaction with ethanol. [redacted] reported that the 23-year-old female's joint pain and swelling (unspecified) increased when she drank red wine. The patient was treated with both OROS methylphenidate HCl and non-Company methylphenidate. Arthralgia and angioedema are known ADRs for OROS methylphenidate HCl. The potential exacerbation of these events during consumption of red wine is not currently known. [redacted] treated with a single dose of sustained release OROS methylphenidate HCl experienced syncope. She was taken to a poison control centre, where blood alcohol level was seen to be 1.5 per thousand (unit not specified) 5.5 hours after exposure to OROS methylphenidate HCl. Dizziness is a listed event in the CCDS for OROS methylphenidate HCl. Lack of information regarding total alcohol consumption, medical history, and concomitant medication precludes adequate assessment. [redacted] who had been receiving OROS methylphenidate HCl for approximately 3 months reported a delusion of being raped after she drank 5 beers (quantity of alcohol not further specified) in 1 evening. No information regarding medical history and concomitant medication was provided, which precludes medical assessment.

In the [redacted] suspected decreased efficacy of OROS methylphenidate HCl after she drank a lot of milky coffee. Efficacy subsequently returned after reduction of her milky coffee intake. This potential food effect has not been described for OROS methylphenidate HCl and the aetiology is likely to be unrelated to milk or dairy product consumption. The indication for use and symptoms experienced were not reported and therefore the possible effect of caffeine on the patient's underlying illness could not be determined.

Patients with no reported age/age category

[redacted] the patient took OROS methylphenidate HCl and antidepressants (unspecified) and subsequently experienced depression, indicating that the drug interaction had led to a LOE for the unspecified medication. The CCDS states that OROS methylphenidate HCl may inhibit the metabolism of some antidepressants (tricyclics and selective serotonin reuptake inhibitors) and downward dose adjustment of these drugs may be required. The lack of information regarding the antidepressant medication, medical history, and concomitant medication precludes any meaningful assessment.

Conclusion

Based on review of cases involving drug or food interaction with OROS methylphenidate HCl that were received within this reporting period, no changes to the CCDS are warranted at this time.

16.2.4. Experience With Overdose, Deliberate or Accidental, and Its Treatment

Introduction

The Overdose Section of the CCDS states *"Signs and symptoms of CONCERTA overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucination (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis, and dry mouth."* Treatment of overdose includes appropriate supportive measures and *"the prolonged release of methylphenidate from CONCERTA should be considered when treating patients with overdose."*

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period, which met PBRER/PSUR reporting criteria, and coded to MedDRA PTs that may involve overdose. Appendix 7.1 provides a listing of terms used to identify these cases.

Results

The search identified 60 medically confirmed cases (50 initial, 10 follow-up; see Appendix 7.3 for AER#s). A review of the follow-up cases did not change the prior assessment of this topic in all 10 cases[64]; these cases are, therefore, not discussed further. Four initial literature cases involved multiple unspecified patients and contained minimal information: [redacted] (Toxicity to various agents, Accidental poisoning) involved multiple children who experienced acute poisoning and reported that OROS methylphenidate HCl was the second most common cause of these drug related poisonings (17.6%, n=24). [redacted] (Drug diversion, Tachycardia, Hypotension, Lethargy, Overdose, Medication error, Overdose) involved multiple patients aged ≤18 years who consumed supratherapeutic amounts of various ADHD medications, of which 42.5% (n=28) occurrences involved OROS methylphenidate HCl; it was not specified which events occurred in association with which drugs (refer to Section 16.2.5, Abuse/Misuse including Diversion). [redacted] (Toxicity to various agents) involved multiple patients of unspecified age who were treated with OROS methylphenidate HCl and on

[redacted]

65 Sahin S, Bora Carman K, Dinleyici EC. Acute Poisoning in Children; Data of a Pediatric Emergency Unit. *Iranian J Pediatr* 2011; 21:479-84.

66 Lo JC, Vo T, Cortez-Gomez B, Cantrell L. A Retrospective Review of Supratherapeutic ADHD Medication Ingestions in Pediatric Patients. Clinical Toxicology 2012 Annual Meeting of the North American Congress of Clinical Toxicology, NACCT 2012; 50:606-607.

67 Hori T. 1-Po-PS2-11 Treatment for Musculoskeletal Tumor with Mental Disorder. *J Japanese Orthopaedic Assoc* 2013; 87:1121.

unspecified dates had drug poisoning. [redacted] involved multiple children or adolescents with ADHD who were treated with OROS methylphenidate HCl and experienced various treatment emergent adverse events. One patient experienced an unspecified overdose with no reported symptoms. The actions taken and outcomes were not reported and these 4 cases are not further discussed.

Table 27 displays a count of the selected PTs by age in the remaining 46 cases received from the current PBRER/PSUR reporting period.

Table 27: Interim Count of Selected PTs by Seriousness in Cases With OROS MPH: Overdose, Deliberate or Accidental

Preferred Term	Number of Events[a,b,c,d]		
Age (years)	**<18[e]**	**≥18[f]**	**NR[g]**
Accidental overdose	1(1)	1 (1)	-(1)
Drug level increased	-(1)		-
Intentional overdose	2	6	-
Multiple drug overdose	-		-
Multiple drug overdose intentional	-		-
Overdose	3(7)	- (2)	-(1)
Prescribed overdose	-(5)	- (6)	-
Toxicity to various agents	2	6	1
Subtotal	**8 (14)**	**13 (9)**	**1(2)**
Total[h]		**46**	

Key: MPH= Methylphenidate hydrochloride; NR= Not reported, PT= Preferred term
a: Cases may have reported more than 1 event of interest.
b: Events reported from medically confirmed cases
c: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified
d: Dash (-) indicates the specified PT was not identified within the age/age group
e: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
f: Includes patients ≥18-years-old and/or patient age category: adult, elderly.
g: Includes patients with no reported age and age category.
h: Includes serious and nonserious events.

Please note that cases in which no AE was associated with the overdose may not appear in the line listings or tabulations appended to the PBRER/PSUR.

[68] Soutullo C, Banaschewski T, Lecendreux M, et al. A post hoc comparison of the effects of lisdexamfetamine dimesylate and osmotic-release oral system methylphenidate on symptoms of attention-deficit hyperactivity disorder in children and adolescents. *CNS Drugs* 2013; 27:743-751.

Of the 46 cases, 14 are presented and discussed elsewhere in this PSUR:

- Five cases[69] resulted in a fatal outcome and are included in Section 16.2.1.1, Cases With Fatal Outcome. Two of these cases [redacted] are further presented in Section 16.2.1.4, Depression and Suicide/Self Injury.
- Nine cases[70] reported a deliberate overdose in the context of a suicide attempt or ideation. These cases are presented in Section 16.2.1.4, Depression and Suicide/Self Injury.

Of the 32 remaining cases identified for further analysis, 23[71] reported overdose with no associated AEs. The overdose PTs reported in these cases were Prescribed overdose (10), Overdose (8), Accidental Overdose (4), and Toxicity to various agents (1). Of these, 10 cases[72] involved patients <18-years-old, 10 cases[73] involved adult patients and in 3 cases ([redacted], [redacted] the ages were not specified; these cases are not discussed further.

Of the remaining 9 cases, 4 described patients who experienced listed events following the overdose and all were in patients <18-years-old. These included hypertension, tachycardia, and nausea in [redacted] ook eleven 27 mg tablets a day "without permission" (it was not specified if it was intentional or accidental); [redacted] reported agitation after an accidental overdose [redacted] and deliberate overdose [redacted] respectively, and [redacted] reported restlessness in a child (age not specified) after an accidental overdose.

The remaining 5 cases are presented below, separated by age group.

Patients <18-years-old

- [redacted] **(*Drug level increased*, Blood creatinine increased):** [redacted] child who was taking OROS methylphenidate HCl 36 mg for ADHD. The patient was also treated with co-suspect non-Company methylphenidate. Concomitant medications were not reported. The patient experienced increased creatinine and drug levels (creatinine 0.99 mg/dL; ritalinic acid 1079 µg/L). The patient recovered from both events. Treatment with OROS methylphenidate HCl was temporarily stopped at the time of the event, but was later reintroduced (see Section 16.3.5.2.4, Use in Children).

[redacted]

- [redacted] **(*Toxicity to various agents*)**: [redacted] treated with OROS methylphenidate HCl for ADHD and behaviour disorder. Co-suspect medication was risperidone. On an unspecified date, the patient was reported to have drug intoxication (methylphenidate), presenting with speech disorder. Laboratory tests were performed but the outcomes not reported. The patient was successfully treated with activated charcoal. The patient recovered. The action taken with OROS methylphenidate HCl was not reported (see Section 16.3.5.2.4, Use in Children).
- [redacted] **(Accidental overdose, *Toxicity to various agents*):** This case involved a [redacted] with ADHD who was treated with co-suspect medication risperidone. The patient took 3 tablets of 36 mg sustained release methylphenidate HCl prescribed for his brother. The patient was noted to be constantly mobile, talked a lot but meaninglessly, not finishing sentences and lisping. The patient went to the emergency paediatric department where methylphenidate intoxication was diagnosed. The patient's vital signs and laboratory assessments were within the normal ranges. The patient was treated with activated charcoal. During the following 48 hours, his symptoms improved, and he had fully recovered. Action taken with methylphenidate HCl was not applicable (see Section 16.3.5.2.4, Use in Children).
- [redacted] **(Dysphoria, Gait disturbance, Disturbance in attention, Headache, Decreased appetite, Malaise, Nausea, Vomiting, Anger, Pyrexia, Blood pressure increased, Treatment noncompliance, *Prescribed overdose*, Influenza)**: [redacted] with hypothyroidism and obesity was treated with OROS methylphenidate HCl initiated at 18 mg, changed to 36 mg, then increased to 54 mg. Since an unspecified date, the patient experienced sickness and nausea "when the higher dose was taken" (which higher dose was not specified). The patient's psychiatrist recommended 54 mg plus 36 mg dose of OROS methylphenidate HCl because the patient was overweight (reported as 74 kg with a height of 150 cm), it is not specified if this dose was actually taken. A dose of 72 mg was initiated and 16 days later the patient was reported to be "feeling better." His symptoms, including a fever, passed and "seemed more like influenza." The dose of 72 mg of OROS methylphenidate HCL was stopped after approximately 4 months, and 72 mg was used "as necessary." The dose of OROS methylphenidate was reported as unchanged, the patient recovered from the events of Disturbance in attention, Headache, Nausea, Vomiting, and Pyrexia, was not recovered from Decreased appetite. The outcome was not reported for Dysphoria, Gait disturbance, Malaise, Anger, Blood pressure increased, Treatment noncompliance, Prescribed overdose, and Influenza (see Section 16.3.5.2.4, Use in Children).

[74] Ekinco O, Celik T, Atilgan A. Highdose methylphenidate and evolving clinical picture; Case report. *Turkish Archives Of Pediatrics.* 2012;47 (Supp.1):105.

[75] Ekinci O, Celik T, Atilgan A. Use of high dose Methylphenidate and the developing clinical profile; a case report. 48th Turkish Congress of Pediatrics-Emergency Pediatrics. 2012:105.

Patients ≥18-years-old

- [redacted] **(Loss of consciousness, *Toxicity to various agents,* Convulsion, Muscle spasms, Incorrect dose administered)**: [redacted] carpel tunnel syndrome was treated with OROS methylphenidate HCl 180 mg/day for ADHD. The patient was also taking non-Company methylphenidate, venlaflaxine, propioazine, levonorgestrel/ethinylestradiol, oxazepam, and desloratadine. The patient was admitted to hospital with generalised cramps and a loss of consciousness. During transportation, the patient experienced a similar "attack" and was treated with diazepam. A head CT was normal, and no neurological problems were detected. The patient was assessed as having a drug-induced cramp. The dose of OROS methylphenidate HCl was decreased, and the patient was followed up in the neurological outpatient department. The patient recovered from the drug intoxication.

Discussion

Nine cases reported AEs in association with an overdose or toxicity to methylphenidate and were therefore reviewed further. Of these, 4 cases described patients who experienced expected AEs following the overdose, and therefore are in line with the current warnings in the OROS methylphenidate HCl CCDS.

In the 5 remaining cases, 4 concerned paediatric patients. [redacted] reported blood creatinine increased in an 11-year-old male treated with both OROS methylphenidate HCl, and non-Company methylphenidate. The total dosage of methylphenidate intake was not reported. The patient fully recovered with temporary interruption to OROS methylphenidate HCl treatment. [redacted] both involved [redacted] with ADHD who experienced an accidental overdose on a single occasion. Both patients were treated with activated charcoal, recovering fully. [redacted] reported nonserious listed and unlisted events in a patient receiving a prescribed overdose; however it was unclear if the patient ever received 54 + 36 mg of OROS methylphenidate HCl. The events appeared to have occurred prior to the dose of 72 mg, and the patient was reported as "feeling better" sixteen days after the 72 mg dose was initiated. The patient was prescribed the overdose due to being overweight; however dosage based on weight is not recommended in the CCDS.

The remaining case involved a female adult. [redacted] treated with OROS methylphenidate HCl 180 mg per day, and also with non-Company methylphenidate (dose not specified); the patient was therefore receiving a greater than recommended dose of OROS methylphenidate HCl, supplemented with additional methylphenidate. The patient experienced loss of consciousness and cramps with no apparent neurological cause, and was described as having drug-induced toxicity. The patient's dose of OROS methylphenidate HCl was reduced and she recovered.

In all cases, the patients recovered from the overdose. In the youngest patients, activated charcoal was used to hasten recovery.

Conclusion

Based on a review of these cases, no new safety signals were identified. The current CCDS adequately describes the symptoms of overdose. No changes to the CCDS are warranted.

16.2.5. Drug Abuse/ Misuse or Medication Error/Maladministration

16.2.5.1. Drug Abuse/Misuse (Including Drug Diversion)

Introduction

The CCDS states that *"[OROS methylphenidate] should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour."* Diversion of OROS methylphenidate HCl is an important potential risk in the RMP and Drug diversion is an unlisted event in the CCDS.

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period, which met PBRER/PSUR reporting criteria, and coded to MedDRA PTs that may involve drug abuse/misuse. Appendix 7.1 provides a listing of terms used to identify these cases. The additional PT Drug diversion was also searched.

Results

The search identified 55 medically confirmed cases (47 initial, 8 follow-up) reporting drug abuse/misuse or drug diversion (see Appendix 7.3 for AER numbers). On review, 15 cases[76] did not involve drug abuse/misuse (including diversion) associated with OROS methylphenidate HCl and are not further discussed. A review of the follow-up information did not change the prior assessment of this topic in all 8 cases[77]; these cases are also, therefore, not discussed further.

Of the initial cases, [redacted] reported the abuse of non-Company methylphenidate; it was not clear if OROS methylphenidate HCl was also abused. [redacted] reported that misuse for weight loss and recreational use "had been known for many years" with no actual patients or events indicated. A further 8 cases involved multiple patients with minimal information relating to the number of patients, events, outcomes, and reason for the abuse.

[redacted]

[redacted]

[78] Aikawa Y. Patients with methamphetamine-related disorders of the third epidemics of methamphetamine abuse in Japan comparison with the second epidemics. *Clin Psychiatry* 2013;42(9):1085-1091.

[79] Richieri R, Adida M, Boyer L, Lancon C. Psychostimulants for treatment of depression. *La Presse Medicale* 2012;42:6.

[redacted] described studies involving abuse or misuse in an unspecified number of patients taking methylphenidate, 2 cases were only observations that there was an increase in misuse of the drug in France [redacted] nd [redacted]) was a meta-analysis of methylphenidate use in Brazil over a decade, and 2 [redacted]) were reviews of the literature to understand the recreational use of methylphenidate. In addition, [redacted]) described multiple events in 20 patients living with daily abuse of drugs and [redacted] reported multiple events occurring following ingestion of methylphenidate in paediatric patients, 28 of whom had taken their sibling's medications (Drug diversion). Two further spontaneous cases involving multiple patients were also retrieved, and described unspecified positive effects in an unspecified number of patients who had tried the medication [redacted] and a suspected case of abuse by healthcare professionals who found residue outside of their facility [redacted]. These 14 cases are also not further discussed.

Table 28 displays a count of the selected PTs by age and seriousness in the remaining 18 cases[88] received from the current PBRER/PSUR reporting period.

[80] Da Rocha Cesar EL, Arantes Wagner G, Castaldelli-Maia JM, Magalhaes Silveira C, Guerra de Andrade A, Garcia de Oliveira L. Prescribed use of methylphenidate hydrochloride and its correlates among Brazilian college students. *Revista de psiquiatria clinica* 2012;39(6):183-188.

[81] Lensing MB, Zeiner P, Sandvik L, Opjordsmoen S. Four-year outcome in psychopharmcologically treated adults with attention-deficit/ hyperactivity disorder: a questionnaire survey. *J Clin Psychiatry* 2013;74(1):e87-e93.

[82] Kim HM, Smith EG, Ganoczy D, et al. Predictors of suicide in patient charts among patients with depression in the Veterans Health Administration health system: Importance of prescription drug and alcohol abuse. *J Clin Psychiatry* 2012;73(10):e1269e1275

[83] La Revue Prescrire. 2012;32:428.

[84] Brant LC, Ferreira Carvalho TR. Methylphenidate: medication as a "gadget" of contemporary life. *Interface Comun. Saude Educ* 2012;16 (42):623-636.

[85] Jensen LS, Dalhoff KP. The pattern of methylphenidate exposures in Denmark. Clinical Toxicology 33rd International Congress of the EAPCCT 2013 Copenhagen Denmark 2013;51(4):340.

[86] Imbert B, Cohen J. Mesusage de Methylphenidate par voie intraveneuse, modalites de consommation, effets secondaires, potentiel addictif, strategies de prise en charge du syndrome de sevrage. 2012;32(1).

[87] Lo JC, Vo T, Cortez-Gomez B, Cantrell L. A retrospective review of supratherapeutic ADHD medication ingestions in pediatric patients. *Clin Toxicol* 2012;50(7):606-607.

[redacted]

Table 28: Interim Count of Selected PTs by Seriousness in Cases With OROS MPH: Drug Abuse/Misuse

Preferred Term	Number of Events[a,b,c,d]		
	Interim 11 October 2012 to 31 October 2013		
Age (years)	**<18[e]**	**≥18[f]**	**NR[g]**
Drug abuse	1	8	-
Drug dependence	-	1	-
Drug diversion	5	1 (2)	1
Intentional drug misuse	- (1)	1	1
Subtotal	**6 (1)**	**11 (2)**	**2**
Total[h]	**22**		

Key: MPH=Methylphenidate hydrochloride; NR=Not reported, PT=Preferred term
a: Cases may have reported more than 1 event of interest.
b: Events reported from medically confirmed cases
c: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified.
d: Dash (-) indicates the specified PT was not identified within the age/age group.
e: Includes patients <18 years old and/or patient age category: neonate, infant, adolescent, child.
f: Includes patients ≥18 years old and/or patient age category: adult, elderly.
g: Includes patients with no reported age and age category.
h: Includes serious and nonserious events.

Of these 18 cases, 9 included the PT Drug diversion. These 18 cases are discussed below.

Drug Abuse

Eight cases reported the potential abuse of OROS methylphenidate HCl (1 patient <18-years-old and 7 patients ≥18-years-old) are discussed here. [redacted] also reported a PT of Drug diversion, and is discussed under Drug diversion.

Patients <18-years-old

[redacted] described an adolescent female who was abusing OROS methylphenidate HCl by snorting the product intranasally after breaking open and crushing the tablets. The patient stated that it gave her a feeling that was "better than using cocaine." It was not reported if the patient was prescribed the drug routinely. The patient's outcome was not reported for drug abuse, possible crushed tablet, and snorted product. No further information, including medical history or duration of abuse, was reported, precluding meaningful assessment (see Section 16.3.5.2.4, Use in Children).

Patients ≥18-years-old

Three cases involved abuse of OROS methylphenidate HCl without additional AEs resulting from the abuse and contained only minimal information; [redacted] described a [redacted] who used the medication as an intoxicant and had a positive result for amphetamine in a drug screen test and [redacted] reported abuse in [redacted] who may or may not have been routinely prescribed with OROS methylphenidate HCl. In case

[redacted] was reported to have been abusing OROS methylphenidate HCl for an unspecified amount of time before switching to bupropion when supply of the tablets depleted. The subsequent abuse of bupropion suggests a history of abuse in this patient.

Three cases described patients with a history of abuse or misuse: [redacted] involved a [redacted] with a medical history of suicidal ideation, suicide attempt, self-injurious behaviour, impulsive behaviour, and alcohol overuse (including simultaneous intake with antidepressant or anti-anxiety medicine) who was prescribed OROS methylphenidate HCl as off label treatment (indication not reported, although concurrent conditions included depressed mood and anxiety) and later reported abuse of the medication based upon the outcome of a 20-point questionnaire. The patient also developed a tendency of dependence on prescribed OROS methylphenidate HCl. The patient was reported to have stopped abusing OROS methylphenidate. [redacted] with a history of multiple drug misuse who injected OROS methylphenidate HCl (Incorrect route of drug administration) along with intake of alcohol. The patient was hospitalised and monitored in the ICU, where slight increases in myoglobin and creatinine were observed; however, the patient was also aggressive and left the ICU before further tests could be carried. Outcome was not reported. [redacted] received from literature[91] and concerned 7 patients in their [redacted] who reported the recreational use of OROS methylphenidate HCl in the year prior to entering a study. The patients had also reported weekly alcohol use (1 patient with abuse) and recreational stimulant use with mixed salt amphetamine, 3,4-methylenedioxymethamphetamine, cocaine, marijuana (2 patients); opioids (1 patient), and benzodiazepines (1). Outcome was not reported.

The remaining case ([redacted] reported abuse with multiple drugs and involved a fatal outcome [redacted] who ingested OROS methylphenidate HCl (Incorrect route of drug administration) along with oxycodone, diazepam, and cocaine with an intent of abuse and died from multiple drug toxicity on an unspecified date (refer to Section 16.2.1.1, Cases with Fatal Outcome).

Following a review of these 8 cases, no specific pattern of drug abuse or dependence was observed for OROS methylphenidate HCl.

[89] Weigand TJ. A cathinone of a different color - Two cases of bupropion abuse presenting with seizures and serotonin syndrome. Clinical toxicology 33rd International Congress of the EAPCCT 2013;51(4):349-350.

[90] Tanibuchi Y, Matsumoto T, Kobayashi O, Wada K. Clinical characteristics of dappou herb use-disorder patients at the drug dependence clinic: a comparison with methamphetamine use-disorder patients. *Psychiatria et Neurologia Japonica* 2013;115(5):463-476.

[91] Stoops WW, Bennett JA, Lile JA, Sevak RJ, Rush CR. Influence of aripiprazole pretreatment on the reinforcing effects of methamphetamine in humans. *ProgrNeuroPsychopharmacol Bioll Psychiatry* 2013;47:111-117.

Drug Misuse

One case reporting misuse of OROS methylphenidate HCl (1 patient ≥18-years-old) is discussed here. Two additional cases reported the PT Intentional drug misuse; [redacted] is discussed under Drug abuse; [redacted] also reported drug diversion and is discussed under Drug diversion.

Patients ≥18-years-old

[redacted] contained only minimal information regarding the circumstances of the misuse and concerned [redacted]) with no reported medical history who misused 1 tablet of OROS methylphenidate HCl on an unspecified date and experienced tachycardia (160 to <170 [units not specified]). It was not reported whether the patient was routinely prescribed with OROS methylphenidate HCl or if the complete dose was taken. No further assessment was possible.

Drug Diversion

Nine cases reporting the PT Drug diversion (5 patients <18-years-old, 3 patients ≥18-years-old, and 1 patient with no reported age/age group) are discussed here.

Patients <18-years-old

Four cases reported from a spontaneous source [redacted] (follow-up [redacted] reported in the previous PSUR) treated with OROS methylphenidate HCl for ADHD who gave his medication to [redacted]) who received 1 tablet of OROS methylphenidate HCl. The students [redacted] and [redacted] were interested in the patient's increased/decreased concentration and impaired appetite. Reported PTs were nonserious: Decreased appetite [redacted] Malaise, Nausea, and Decreased appetite [redacted] and Therapeutic response unexpected [redacted]. [redacted] reported no additional AEs. Refer to Section 16.3.5.2.4, Use in Children.

[redacted] who missed a dose of OROS methylphenidate HCl as no medication was available due to "being taken or stolen by someone at home". No further details were provided as to the possible drug diversion. Four days after his last dose, the patient experienced headache, paleness, feeling down, and nausea. Outcome for the events was not reported (refer to Section 16.3.5.2.4, Use in Children).

Patients ≥18-years-old

[redacted] was received from literature,[92] and concerned an [redacted] who had taken OROS methylphenidate HCl (possible abuse) that he had purchased from others (drug diversion). The patient had a long history of stimulant abuse, beginning in his late teens with crack cocaine and continuing into his late 30s with heavy use of methamphetamine and several instances of abuse of bupropion.

The remaining 2 cases in this age group involved patients who received a dose of OROS methylphenidate HCl from a friend: [redacted] with adrenoleukodystrophy who reported that the symptoms of his disease improved distinctly with OROS methylphenidate HCl (unexpected therapeutic benefit) and [redacted] reported that [redacted] took only 1 tablet of OROS methylphenidate HCl 36 mg to help concentrate during studying and experienced tachycardia on an unspecified date. Outcome was not reported in either of these cases.

Patient age not reported

[redacted] concerned a patient (age and sex not reported) without a prescription for OROS methylphenidate HCl who dissolved the coating from the tablets in water and injected the solution (Wrong technique in drug usage process). It was not known how the patient had got a hold of the coating and therefore a possible Drug diversion was also reported. Whether the patient continued to inject OROS methylphenidate HCl and outcome of the event was not reported. No further details were provided.

Conclusion

Based on the review of the cases received during this reporting period, no changes to the CCDS or RMP are warranted at this time.

16.2.5.2. Medication Error/Maladministration

Introduction

The Dosage and Administration Section of the CCDS states that "*CONCERTA is administered orally once daily. As the effect has been shown to be present 12 hours after dosing, the product should be taken once daily in the morning. CONCERTA must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed".* It also states that *"Because the [OROS methylphenidate HCl] tablet is non-deformable and does not appreciably change in shape in the GI tract, [OROS methylphenidate HCl] should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Due to the controlled-release design of the tablet, [OROS methylphenidate HCl] should only be used in patients who*

[92] Reeves RR, Ladner ME. Additional evidence of the abuse potential of bupropion. *J Clin Psychopharmacol* 2013;33(4):584-585.

are able to swallow the tablet whole." Furthermore, the CCDS recommends the maximum daily dose of 54 mg in children, 72 mg in adolescents, and 108 mg in adults.

According to the RMP, Off label use is an important potential risk associated with use with OROS methylphenidate HCl.

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period, which met PBRER/PSUR reporting criteria, and coded to MedDRA PTs that may involve medication error/maladministration. Appendix 7.1 provides a listing of terms used to identify these cases.

Results

A total of 203 medically confirmed cases (187 initial, 16 follow-up) reporting medication error/maladministration were received during the reporting period (see Appendix 7.3 for AER numbers).

Of the 16 follow-up reports, 1 spontaneous [redacted] concerned multiple, unidentifiable patients; the physician, who worked in a jail setting, suspected that some of the inmates were using OROS methylphenidate HCl intra-nasally (snorting); no further information relating to the event or patients was reported. A review of the follow-up information in 10 cases[93] did not change the prior assessment of this topic, these cases are therefore, not discussed further. [redacted] reported new medication error PTs, Off label use (3), Drug dose omission (2), and Drug prescribing error (2) and are included for further review.

Of the 187 initial cases, 18 literature cases[94] (refer to Appendix 7.4 for literature references) involved multiple, unidentifiable patients and reported the following PTs: Off label use (12 cases), Incorrect route of drug administration (3 cases), Incorrect dose administered (2 cases), Medication error (2 cases), and 1 case each of Accidental exposure, Drug dispensing error, and Inappropriate schedule of drug administration. Of these 18 cases, 3 cases involved multiple, [redacted] involved a study to understand the characteristics of supratherapeutic ADHD medication exposure in 301 patients. Medication error, including taking a sibling's medication (9.3%), and dispensing error (8.3%) were reported; [redacted] reported the PT Drug dispensing error (mix-up between OROS methylphenidate HCl and methadone) in an unspecified number of patients, and case [redacted] involved the Off label treatment of narcolepsy and cataplexy in 13 patients. Four cases involved multiple adult patients: [redacted] reported Off label use for depressive anxiety disorder; [redacted] concerned an analysis of the use of

[redacted]

[redacted]

OROS methylphenidate HCl and methylphenidate HCl in approximately 20,000 patients over a year in Denmark. It was reported that some patients used OROS methylphenidate HCl unintentionally, some used it for recreational purposes, and some used it for suicide attempts; [redacted] who had daily abuse of drugs and it was reported that OROS methylphenidate HCl was administered via intravenous route (Incorrect route of drug administration), and [redacted] involved multiple, imprisoned male adults who were administered more than the recommended dose. Ten multiple patient cases did not specify the age group: [redacted] reported the non-medical use of OROS methylphenidate HCl, including the Off label use for weight loss, and for recreational purposes; [redacted] reported Off label use for depression; 4 cases [redacted] concerned the use of methylphenidate for the Off label treatment of cancer and/or cancer-related symptoms; [redacted] involved an analysis of a number of different publications and reported the PT Drug prescription error (excess prescription); [redacted] reported failure in treatment in an unspecified number of patients because of Medication errors (low adherence to correct use of medication) and Medication intolerance; [redacted] involved the broad forensic screening of analytes in an unspecified number of subjects charged with driving under the influence of which methylphenidate appeared (Incorrect dose administered). [redacted], reporting the PT Off label use (drug use in an unapproved population), involved an analysis of cardiac events experienced in a cohort of 30,576 paediatric patients and young adult patients [redacted]. In all these cases, limited information relating to patient demographics, dosage, latency, details regarding the event and outcome were provided, precluding adequate medical assessment. This is also the case for 5 spontaneous cases [redacted] received from physicians, nurses or other healthcare professional, which concerned multiple, unidentifiable patients. [redacted], involving paediatric patients and [redacted] concerning adult patients reported the PT Off-label use; [redacted]) reported Incorrect dose administered (double dose and more than the recommended dose, respectively), and [redacted], involving patients of an unspecified age, reported Off label use and Incorrect route of drug administration. These cases provided very limited information and are also not discussed further.

Table 29 displays a count of the selected PTs by age and seriousness in the remaining 169 cases (164 initial and 5 follow-up) included for further analysis received from the current PBRER/PSUR reporting period.

Table 29: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Medication Error and Maladministration

Preferred Term	Number of Events[a,b]		
Age (years)	**<18[c]**	**≥18[d]**	**NR[e]**
Accidental exposure to product	1 (3)	- (1)	-
Accidental exposure to product by child	- (1)	-	-
Contraindication to medical treatment	- (1)	- (1)	-
Drug administration error	- (1)	- (1)	-
Drug dispensing error	1	- (1)	- (2)
Drug dose omission	- (16)	- (2)	- (6)
Drug name confusion	- (1)	-	-
Drug prescribing error	- (8)	- (10)	- (7)
Expired drug administered	-	-	- (1)
Inappropriate schedule of drug administration	- (2)	1 (6)	- (2)
Incorrect dosage administered	- (1)	-	-
Incorrect dose administered	- (11)	- (6)	- (3)
Incorrect drug administration rate	-	-	- (1)
Incorrect drug dosage form administered	-	- (1)	-
Incorrect storage of drug	-	-	- (1)
Incorrect route of drug administration	-	2	-
Medication error	- (7)	- (2)	- (1)
Off label use	- (18)	- (30)	- (7)
Poor quality drug administered	- (2)	- (1)	- (2)
Treatment noncompliance	- (9)	- (4)	- (2)
Wrong drug administered	-	- (1)	-
Wrong technique in drug usage process	- (11)	- (4)	- (7)
Subtotal	**2 (92)**	**3 (71)**	**- (42)**
Total[f]	**210[g]**		

Key: MPH=Methylphenidate hydrochloride; NR=Not reported, PT=Preferred term

a: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified

b: Dash (-) indicates the specified PT was not identified within the age/age group

c: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child

d: Includes patients ≥18-years-old and/or patient age category: adult, elderly

e: Includes patients with no reported age and age category.

f: Includes serious and nonserious events.

g: Some cases report more than 1 PT of interest

An overview of the characteristics of the 169 cases included for further review (78 patients < 18-years-old, 57 patients ≥ 18-years-old, and 34 patients with no reported age/age category) is presented in Table 30, Table 31, and Table 32, respectively.

Table 30: Characteristics for OROS MPH in Selected Cases Reporting Medication Error in Patients <18-years-old

Characteristics		Number of Cases (n=78)
Sex	Male	52
	Female	17
	Not reported	9
Age (years)	<5	4
	≥5 to <9	14
Mean: 10.8	≥9 to ≤13	26
Median: 11.0	>13 to <18	20
	Child	10
	Adolescent	4
Daily Dose	20 mg	1
	18 mg	16
	27 mg	15
	36 mg	11
	54 mg	10
	63 mg	1
	72 mg	4
	81 mg	1
	99 mg	1
	108 mg	2
	162 mg	1
	"1 dose"	1
	"2 doses"	1
	Not reported	13
Indication[a]	ADHD	43
	Asperger's disorder	3
	Abnormal behaviour	2
	Autism spectrum disorder	1
	Disturbance in social behaviour	1
	Malaise	1
	Mental disability	1
	Narcolepsy	1
	Psychomotor hyperactivity	1
	Not reported	26
Outcome of Event of Interest[b]	Recovered/Resolved	6
	Not Recovered/Not Resolved	9
	Not reported	79

Key: ADHD=Attention Deficit Hyperactivity Disorder; MPH=Methylphenidate hydrochloride; n=Number of cases

a: Some cases reported more than 1 indication

b: Some cases reported more than 1 PT of interest

Table 31: Characteristics for OROS MPH in Selected Cases Reporting Medication Error in Patients ≥18-years-old

Characteristics		Number of Cases (n=57)
Sex	Male	32
	Female	18
	Not reported	7
Age (years)	≥18 to 30	26
	31 to 50	20
Mean: 34.4	51 to 65	3
Median: 30.5	>65	3
	Adult	5
Daily Dose	10 mg	1
	18 mg	6
	20 mg	3
	27 mg	1
	36 mg	7
	54 mg	5
	72 mg	7
	108 mg	3
	144 mg	1
	162 mg	1
	180 mg	2
	270 mg	1
	324 mg	1
	Not reported	18
Indication[a]	ADHD	19
	Adrenoleukodystrophy	1
	Depression	1
	Drug abuse	1
	Fatigue	1
	Head injury	1
	Narcolepsy	1
	Obsessive-compulsive disorder	1
	Off label use	1
	Social phobia	1
	Somnolence	1
	Not reported	31
Outcome of Event of Interest[b]	Fatal	1
	Recovered/Resolved	4
	Not Recovered/Not Resolved	5
	Not reported	64

Key: ADHD=Attention Deficit Hyperactivity Disorder; MPH=Methylphenidate hydrochloride; n=Number of cases

a: Some cases reported more than 1 indication

b: Some cases reported more than 1 PT of interest

Table 32: Characteristics for OROS MPH in Selected Cases Reporting Medication Error in Patients With No Reported Age/Age Category

Characteristics		Number of Cases (n=34)
Sex	Male	13
	Female	6
	Not reported	15
Daily Dose	18 mg	4
	36 mg	7
	45 mg	1
	50 mg	1
	54 mg	6
	72 mg	1
	108 mg	1
	135 mg	1
	162 mg	1
	648 mg	1
	Not reported	10
Indication	ADHD	9
	Autism	1
	Central nervous system stimulation	1
	Fatigue	1
	Narcolepsy	1
	Not reported	21
Outcome of Event of Interest[a]	Not Recovered/Not Resolved	5
	Not reported	37

Key: ADHD=Attention Deficit Hyperactivity Disorder; MPH=Methylphenidate hydrochloride; n=Number of cases
a: Some cases report more than 1 PT of interest

Of the 210 medication error/maladministration events reported, 205 were nonserious. The following PTs were reported: Off label use (55), Drug dose omission (24), Drug prescribing error (25), Wrong technique in drug usage process (22), Incorrect dose administered (20), Treatment noncompliance (15), Inappropriate schedule of drug administration (10), Medication error (10), Poor quality drug administered (5), Accidental exposure to product (4), Drug dispensing error (3), Contraindication to medical treatment (2), Drug administration error (2), and 1 each of Accidental exposure to product by child, Drug name confusion, Expired drug administered, Incorrect dosage administered, Incorrect drug administration rate, Incorrect drug dosage form administered, Incorrect storage of drug, and Wrong drug administered.

There were 53 cases (see Appendix 7.3 for AER numbers) reporting 55 Off label use PTs (2 cases reported the PT Off label use twice). Of these, 18 cases[95] involved patients <18-years-old. Nine of these cases[96] included the following off label use: Asperger's disorder (3), Abnormal behaviour (1), Autism spectrum disorder (1), Malaise (1), Mental disability (1), Narcolepsy (1), and Psychomotor hyperactivity (1). Three cases reported the indication of

[redacted]

[redacted]

ADHD but characterised drug use in an unapproved indication: in [redacted], 18 mg OROS methylphenidate HCl was prescribed to [redacted] (age not specified) who was unable to swallow the tablet and the patient's caregiver divided the tablet before use; the patient experienced logorrhoea and medication was stopped; [redacted] involved a [redacted] prescribed with OROS methylphenidate HCl 18 mg daily and then 27 mg daily. The dose was reduced back to 18 mg due to loss of appetite; [redacted] also involved the [redacted] treated with 18 mg which was increased to 27 mg daily, resulting in loss of appetite and OROS methylphenidate HCl was reduced back to 18 mg. Two cases reported the use of OROS methylphenidate HCl for ADHD and another indication: in [redacted] it was also prescribed to [redacted] for ADHD and disruptive behaviour problems and in [redacted] it was prescribed to a [redacted] for ADHD and autism.

[redacted] off label use in patients <18-years-old did not provide the indication for use. Two of these cases involved patients <6 years old, characterising drug use in an unapproved population: in [redacted] OROS methylphenidate HCl 18 mg was prescribed for [redacted] and in [redacted] OROS methylphenidate HCl 63 mg was prescribed to [redacted]. In [redacted] had a prescribed overdose of 72 mg; and [redacted] an adolescent female prescribed 27 mg OROS methylphenidate HCl for an unspecified indication.

Twenty-five cases[97] reported off-label use in adult patients. Of these, 7 cases[98] reported the following off label use indications: Adrenoleukodystrophy (1), Depression (1), Drug abuse/Fatigue (1), Head injury (1), Obsessive-compulsive disorder (1), Off label use (1), and Somnolence (1). [redacted] reported the indication of ADHD in addition to narcolepsy. Nine cases[99] did not report the indication for use (although 1 of these cases [redacted] did report a history of ADHD, depression, and stress at work and 1 case [redacted] reported a history of anxiety, depressed mood, impulsive behaviour, and self-injurious behaviour). Eight cases[100] involving adults reported the indication as ADHD: 7 of these cases involved dosages in an unapproved population; and 1 [redacted] reported contraindicated use (patient with history of cardiovascular or cerebrovascular history).

[redacted]

There were 7 cases[101] in which the off label use involved patients with an unspecified age/age group, 3 of these cases [redacted] reported the off label indications central nervous system stimulation, autism, and narcolepsy, respectively. Two cases ([redacted] did not report the indication, and 2 cases reported the indication of ADHD: in [redacted] drug use in an unapproved population was characterised and in [redacted] the Off label use was not specified.

There were 5 medication error events reported to be serious: Incorrect route of drug administration (2), Accidental exposure to product (1), Drug dispensing error (1), and Inappropriate schedule of drug administration (1). Two of these cases involved patients <18-years-old and 3 cases involved adult patients. [redacted] which reported the PT Incorrect route of drug administration, reported [redacted] death due to intentional multiple drug toxicity with OROS methylphenidate HCl, oxycodone, diazepam and cocaine and is discussed in Section 16.2.1.1, Cases With Fatal Outcome. Of the 2 cases involving patients <18-years-old, [redacted]) involved [redacted] who had accidental exposure to OROS methylphenidate HCl. The patient took 2 doses within [redacted] a [redacted] who was inadvertently dispensed methadone instead of OROS methylphenidate HCl. The bottle was labelled as OROS methylphenidate HCl 10 mg, and the patient's mother gave the medication to the child as prescribed. The patient became lethargic and vomited after taking 1 dose. The same symptoms developed again after giving the child the twice daily dose the following day and he was admitted to intensive care for treatment, after which he recovered.

The 2 remaining cases (both spontaneous) involving adult patients are described below.

- [redacted] **(Poisoning, Drug abuse, *Incorrect route of drug administration*, Aggression, Blood creatinine increased, Myoglobin blood increased)**: [redacted] with a history of ADHD, hepatitis C, and multiple drug misuse injected OROS methylphenidate HCl dissolved in ethanol (it was not specified if the patient was routinely prescribed OROS methylphenidate HCl). The patient experienced intoxication and was admitted to the ICU for monitoring. Laboratory tests showed a slight increase in myoglobin and increased creatinine but there was no time to perform further observations as the patient was agitated (aggressive) and refused to stay at the ICU. The outcome was not reported (see also Section 16.2.5.1, Drug Abuse/Misuse).
- [redacted] **(Weight decreased, Heart rate increased, *Inappropriate schedule of drug administration*):** [redacted] was treated with OROS methylphenidate HCl (sustained release tablets, oral) for an unspecified indication. The patient took 27 mg to 36 mg depending on how he felt for over a year, characterising inappropriate schedule of

[redacted]

[102] Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC. 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. *Clin Toxicol*. 2012;50:911-1164.

[103] Gaunt MJ. Mix-ups Between Methylphenidate and Methadone Impact Children and Adults. *Pharmacy Times* 2013;79(8):44.

drug administration. It was reported that the patient had been exercising "a fair bit lately" and experienced increased heart rate, measured at the general practitioner's office as 170 beats per minute. The patient also lost 8 kg (weight loss) in a week which was unusual for him. OROS methylphenidate HCl was withdrawn and his heartbeat returned to normal.

Discussion

In the 169 cases identified for further review there were 205 medication error events reported which were considered nonserious. Of these, 53 cases reported 55 events of Off label use; the majority of these cases reported an unspecified indication, and there were no patterns observed among the other reported Off label indications. The CCDS states "*CONCERTA is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of CONCERTA in the treatment of ADHD was established in controlled trials of children and adolescents aged 6 to 17 and adults aged 18 to 65 who met DSM-IV criteria for ADHD.*"

There were 5 serious medication error events reported in 5 cases.

Patients <18-years-old

Two cases reported serious medication error events in patients <18-years-old. [redacted] reported a drug prescribing error of methadone which had been inadvertently dispensed in a bottle with an OROS methylphenidate HCl label resulting in lethargy and vomiting in a 7-year-old male. [redacted] the inappropriate schedule of administration (2 doses within 90 minutes) did not result in any symptomatic AEs in the 11-year-old male. Refer to Section 16.3.5.2.4, Use in Children.

Patients ≥18-years-old

Three cases reported serious medication error events in adult patients. In 1 of the cases [redacted] event had an outcome of death reported due to multiple drug toxicity; the patient's medical history was not reported in this case, precluding adequate medical assessment. Of the 2 remaining cases reporting serious medication error events, [redacted] reported an incorrect route of drug administration (intravenous) and was confounded by the patient's history of drug abuse. [redacted] reported an inappropriate schedule of drug administration (27 mg to 36 mg depending on his condition). According to the CCDS for OROS methylphenidate HCl, this is within the recommended dosage for an adult patient currently using methylphenidate.

Conclusion

Review of these cases does not provide evidence that represent a new safety concern. No changes to the CCDS or RMP are warranted at this time.

16.3. Evaluation of Risks and New Information

Analysis of Topics for Review

All events received during the reporting period are reviewed. Cases reporting a fatal outcome[104] and topics of special interest are discussed regardless of listedness. Considerations for identifying topics of interest may include, but are not limited to, identified trends, changes in reporting frequency, possible risk factors, changes in severity or seriousness of events, previously defined topics of interest and/or regulatory requests/commitments.

A frequency tabulation of MedDRA PTs reported for OROS methylphenidate HCl during the reporting period was reviewed to identify topics for review. MedDRA PTs and/or a SMQ related to the specific topic were selected. The GMS safety database was then searched to retrieve medically confirmed cases reporting the PTs/SMQs.

16.3.1. New Information on Important Identified Risks

Important identified risks are summarised in the OROS methylphenidate HCl CCDS and EU-RMP, with the exception of the identified risks confirmed after this reporting period of priapism and increased libido. Refer to Section 16.2, Signal and Risk Evaluation.

16.3.2. New Information on Important Potential Risks

No new safety information on potential risks was identified during the reporting period HCl.

16.3.3. New Information on Other Identified Risks not Categorised as Important

No new safety information was identified during the reporting period.

16.3.4. New Information on Other Potential Risks not Categorised as Important

No new safety information was identified during the reporting period.

16.3.5. Update on Important Missing Information

No new safety information was identified during the reporting period.

16.3.5.1. Positive and Negative Experience During Pregnancy or Lactation

Introduction

According to the CCDS, *"The safety of methylphenidate for use during human pregnancy has not been established. No studies are available on the use of CONCERTA in pregnant women. CONCERTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."* It further states, "*It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA is administered to a nursing woman."*

[104] Cases with an outcome of Fatal or reporting selected PTs (see Appendix 7.1).

Methods

The GMS safety database was searched for all medically confirmed cases received during this reporting period that may involve exposure during pregnancy or lactation. Appendix 7.1 provides a listing of terms used to identify these cases.

Results/Discussion

A total of 16 medically confirmed initial cases[105] (no follow-up) involving exposure during pregnancy or lactation were received during this reporting period. These 16 medically confirmed cases represented 15 pregnancies (15 maternal cases, 1 paternal case, and no infant cases). There were no cases reporting lactation disorders. Of these 16 cases, 10 cases[106] reported nonserious maternal drug exposure during pregnancy with no additional AEs and no pregnancy outcomes; [redacted] was reported as serious but limited information about the case precludes further medical ass[redacted]ssment and no pregnancy outcome was reported. In 5 of these cases,[107] treatment with OROS methylphenidate HCl was stopped on discovery of the pregnancy, which was reported as ongoing. Please note that cases in which pregnancy exposure was the only reported event do not appear in the line listings or tabulations appended to the PBRER/PSUR.

Case 20120600094 reported Exposure during pregnancy with no additional AEs and the patient delivered a mature baby of [redacted]

[redacted] a negative human chorionic gonadotropin qualitative test (hCG) was obtained. On an unspecified date, treatment with OROS methylphenidate HCl was stopped. Thirteen days after the negative hCG test, the subject was diagnosed as 5 weeks pregnant, and underwent an induced abortion 13 days later.

The remaining 3 cases reported additional AEs and are discussed below.

- [redacted] **(Abortion spontaneous, Uterine dilation and curettage, Foetal death, Exposure during pregnancy):** [redacted] was treated with OROS methylphenidate HCl for ADHD. Concomitant medications were not reported. She had 3 previous normal pregnancies. During treatment with OROS methylphenidate HCl, the patient had become pregnant 3 times and on each occasion lost the foetus. She discontinued treatment with OROS methylphenidate HCl on each occasion 4 to 6 weeks prior to the spontaneous abortions as she suspected that she was pregnant. At the time of the report, the patient was in the 17th week of another pregnancy, the course of which was normal. It was reported that the patient had not taken OROS methylphenidate HCl during the current pregnancy. No further information was available on the outcome of the pregnancy. The

[redacted]

relationship between the events of spontaneous abortion and OROS methylphenidate HCl treatment was considered as possible.

- [redacted] **(Abortion spontaneous, Exposure via father) and linked [redacted] (Pregnancy of partner):** [redacted] whilst [redacted] Concomitant medications were not reported. On an unspecified date, the patient had a miscarriage. The date of the patient's last menstrual period and expected delivery date were not reported. No further information was available.

The 3 cases included for further review (including 2 linked cases) provided limited information for adequate medical assessment. No cases of spina bifida associated with OROS methylphenidate HCl administration during pregnancy were received in the reporting period.

Conclusion

Based on this review, no changes to the CCDS are warranted at this time.

16.3.5.2. Experience in Special Patient Groups

Cases involving the use of OROS methylphenidate HCl in patients with renal dysfunction or hepatic dysfunction, as well as in elderly and paediatric patients are reviewed in all PBRERs/PSURs.

16.3.5.2.1. Renal Dysfunction

Introduction

According to the Dosage and Administration/Special Populations Section of the CCDS*:* "*There is no experience with the use of CONCERTA in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of [(alpha)-phenyl-piperidine acetic acid]. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA.*"

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period, which met PBRER/PSUR reporting criteria, and reported medical history suggestive of renal dysfunction (see Appendix 7.1 for selected terms).

Results/Discussion

Six initial cases[108] (no follow-up) involving patients with pre-existing renal disorders were received during the reporting period. [redacted], from literature, reported the nonserious events of Weight decreased and Decreased appetite in [redacted] with a medical history of ADHD, Noonan syndrome, 1 non-functioning kidney, pulmonary valve stenosis, atrial septal defect, otitis media, and pulmonary lymphangiectasia, unspecified renal disorder and treatment with growth hormone for growth retardation. Treatment with OROS methylphenidate HCl was withdrawn and the patient recovered from Weight decreased (outcome not specified for [redacted]reased appetite). [redacted] the nonserious events of Prescribed overdose and Drug effect decreased [redacted] with a medical history of ADHD, diabetes mellitus, blindness, dialysis, drug abuse, leg amputation, nervousness, psychotic disorder and restlessness. The patient received OROS methylphenidate HCl 144 mg daily for about a year with good effect. On an unspecified date, ADHD symptoms were reportedly worse following dialysis. Action taken with OROS methylphenidate HCl and outcome were not reported. [redacted] reported the serious events of Hallucination, Extrapyramidal disorder, and Aggression, and the nonserious events of Laryngitis, Somnolence, Diplopia, Headache, and Abdominal pain upper in a [redacted] with a medical history of ADHD, nephrotic syndrome, and hypersensitivity. The patient became symptomatic on an unspecified date after switching from methylphenidate hydrochloride 10 mg BID for several years to OROS methylphenidate HCl 36 mg. He was treated with diazepam and recovered. [redacted] reported the nonserious event of Renal function test abnormal in a patient (age and sex unspecified) with a medical history of renal atrophy. The patient had been treated for with OROS methylphenidate HCl for ADHD for approximately 1 year. Action taken with OROS methylphenidate HCl and outcome were not reported. [redacted] reported the nonserious event of Drug ineffective in a male patient of unspecified age with a medical history of haemodialysis who was treated with OROS methylphenidate HCl 54 mg/day. Action taken with OROS methylphenidate HCl and outcome were not reported. Case 20130903097 reported the nonserious event of Exposure during pregnancy in a 17-year-old female with a medical history ADHD, hydronephrosis, alcohol use, substance use, tobacco use, and urinary tract infection. OROS methylphenidate HCl was discontinued. Foetal condition was reportedly normal. The final outcome of the pregnancy was not reported (refer to Section 16.3.5.1, Positive and Negative Experience During Pregnancy or Lactation).

Conclusion

Based on the review of these cases, no changes to the CCDS are warranted.

[redacted]

[109] Mushtaq I, Matras B, Huzair H. A case of ADHD in a patient with Noonan syndrome. *Prog Neurol Psychiatry* December 2012;16(6):16-17

16.3.5.2.2. Hepatic Dysfunction

Introduction

According to the Dosage and Administration/Special Populations Section of the CCDS: "*There is no experience with the use of CONCERTA in patients with hepatic insufficiency.*"

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period, which met PBRER/PSUR reporting criteria, and reported medical history suggestive of hepatic dysfunction (see Appendix 7.1 for selected terms).

Results/Discussion

Four initial cases ([redacted] involving patients with pre-existing hepatic disorders were received during the reporting period.

Two of these cases, involving patients <18-years-old, reported hepatic events. [redacted] with a history of hepatomegaly who experienced severe Hyperbilirubinaemia and Hypertransaminasemia approximately 2 months after initiating treatment. Concomitant medications were not reported. Action taken with OROS methylphenidate HCl and event outcomes were not reported. [redacted] with a history of Gilbert's syndrome with a little jaundice who experienced worsening of pre-existing Jaundice while being treated with OROS methylphenidate HCl 36 mg therapy for 1 month for ADHD. Concomitant medication included atomoxetine. The dose of OROS methylphenidate HCl was not changed and the outcome for worsened Jaundice was not reported.

The 2 remaining cases involved adult patients. [redacted] with a history of unspecified hepatopathy who experienced the serious unlisted event of Papilloedema and Visual acuity reduced 4 months after receiving his last dose of OROS methylphenidate HCl 54 mg for ADHD. Co-suspect medications included purethal. Concomitant medications were not reported. Action taken with OROS methylphenidate HCl and event outcomes were not reported. [redacted] with a history of hepatitis C and multiple drug misuse (unspecified) who experienced the serious unlisted events of Poisoning, and Drug abuse, and the nonserious events of Aggression, Blood creatinine increased, and Myoglobin blood increased on the same day as commencing treatment with OROS methylphenidate HCl for an unspecified indication. The patient injected OROS methylphenidate HCl dissolved in co-suspect ethanol (Incorrect route of drug administration). The patient was hospitalised and monitored in intensive care unit (ICU); however, he became aggressive, refused to stay, and left the ICU. Event outcomes and action taken with OROS methylphenidate HCl were not reported (see Section 16.2.5.2, Medication Error/Maladministration and Section 16.2.5.1, Drug Abuse/Misuse).

Conclusion

Based on the review of these 4 cases, no changes to the CCDS are warranted.

16.3.5.2.3. Use in Elderly

Introduction

According to the Dosage and Administration/Special Populations Section of the CCDS, "*Use of [OROS methylphenidate HCl] in elderly patients over 65 years of age has not been studied in controlled trials.*"

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period that met PBRER/PSUR reporting criteria and where the patient's age was ≥65 years or the patient age group was elderly.

Results/Discussion

Seven medically confirmed cases[110] (6 initial, 1 follow-up) involving elderly patients were received during the reporting period. [redacted] reported a new event of Off label use in the current reporting period and is included for analysis. Initial literature case [redacted] involved non-Company methylphenidate and is not included for further review.

The ages in the remaining 6 cases ranged from 66 to 95 years (mean: 73.8 years, median: 71.0 years) and reported the following 13 PTs: Off label use (4), Toxicity to various agents (3), Completed suicide (2), and 1 each for the following: Contraindication to medical treatment, Depression, Drug ineffective, and Dyskinesia. The indications reported for OROS methylphenidate HCl use were: depression (2 cases), unspecified indication (2 cases), and 1 case each of suicide attempt and ADHD. Three literature cases received from the same article ([redacted] reported fatal outcomes and are discussed in Section 16.2.1.1, Cases with Fatal Outcome. [redacted] are also included in Section 16.2.1.4, Depression and Suicide/Self injury.

Conclusion

Based on the review of these cases, no changes to the CCDS are warranted.

16.3.5.2.4. Use in Children

Introduction

According to the CCDS, *"Use of CONCERTA in patients under six years of age has not been studied in controlled trials. CONCERTA should not be used in patients under six years old" and*

[redacted]

[111] Yagihara K, Okabe S, Nakayama R, Ishii J. A case of oral cancer who developed neuroleptic malignant syndrome due to methylphenidate hydrochloride used to shake off sleepiness for opioid. *Oral Thera Pharmacol* 2011;30 (3):97-102.

[112] Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC. 2011 Annual report of the American Association of Poison Control Centers National Poison Data System (NPDS): 29th Annual report. *Clin Toxicol* 2012;50:911-1164.

"Daily dosages above 54 mg in children, 72 mg in adolescents….have not been studied and are not recommended."

OROS methylphenidate HCl is indicated for use in children and adolescents aged 6 to 17 years. All of the topics reviewed in the PSUR focus on use in paediatric patients.

Methods

The GMS safety database was searched for medically confirmed cases received during this reporting period that met PBRER/PSUR reporting criteria and where the patient age was <18 years or the patient age group was neonate, infant, child or adolescent.

Results/Discussion

A total of 588 cases (541 initial, 47 follow-up; see Appendix 7.3 for AER#s) involving paediatric patients <18 years of age and/or age group neonate, infant, child, and adolescent were received during the reporting period.

Thirty-three of the follow-up cases (see Appendix 7.3 for AER#s) did not provide new safety information; therefore, these cases are not discussed further. The remaining 14 follow-up cases contained relevant new information, including the age of the patient [redacted] event causality assessment changed to very likely/certain ([redacted] and a new event during the current reporting period (8 cases[113]).

Seventeen[114] initial cases, including 8[115] literature cases (see Appendix 7.4 for list of references), concerned multiple unidentifiable patients and contained minimal information, of which [redacted] are summarised in Section 16.2.5.2, Medication errors and maladministration, [redacted]) is summarised in Section 16.2.5.1, Drug abuse/Misuse, [redacted]) are summarised in Section 16.2.2, Efficacy-related information, and [redacted]) is summarised in Section 16.2.4, Experience With Overdose, Deliberate or Accidental, and Its Treatment. The PTs reported in the remaining 9 cases were as follows: [redacted] (Mean cell volume increased), [redacted] (Raynaud's phenomenon), [redacted] (Miosis), [redacted] and [redacted] (Breath odour), [redacted] (Somnolence, Decreased appetite, Weight increased, Hyperprolactinaemia, Weight decreased, Insomnia, Headache), [redacted](Tic, Insomnia, Staring, Social avoidant behaviour, Decreased interest, Decreased appetite, Irritability, Abdominal pain upper, Headache, Somnolence, Depressed mood, Crying, Anxiety, Onychophagia, Euphoric mood), [redacted]

[redacted]

(Negativism), and [redacted] (Depression). None of these 17 cases provided information regarding dose, onset latency, action taken, or outcome and are not discussed further.

In the remaining 538 cases, 12 reported an age <6 years or age group neonate or infant, 449 reported an age between 6 and 17 years, and 77 reported the age category of child or adolescent.

Of the 12 cases[116] reporting an age <6 years (OROS methylphenidate HCl is not approved for use in this population), 7 were males, 3 were females, and in 2 cases sex was not reported. Ages ranged from 1 to 5 years (median 4.0 years). OROS methylphenidate HCl was indicated for ADHD (3), and 1 each for Accidental exposure to product, Abnormal behaviour, Disturbance in social behaviour, and Mental disability.[117] In 7 cases the indication was not specified. Seven cases reported more than 1 event.

The frequency of PTs reported in these 12 cases is presented in Table 33.

Table 33 PTs Reported in OROS MPH Paediatric Patients <6 Years of Age and/or Age Category of Neonate and Infant

MedDRA PT	Number of Events (Cases)[a]
Off label use	4
Drug prescribing error	2
Feeling abnormal	2
Irritability	2
Tearfulness	2
Toxicity to various agents	2
Accidental exposure to product	1
Accidental exposure to product by child	1
Accidental overdose	1
Aphagia	1
Decreased appetite	1
Drug ineffective	1
Dysphagia	1
Incorrect dose administered	1
Urinary incontinence	1
Total	**23 (12)**

Key: MedDRA=Medical Dictionary for Regulatory Activities, MPH= Methylphenidate hydrochloride, PT= Preferred term
a: Cases may report more than 1 PT

Of the 449 cases reporting an age 6 to 17 years, 333 were males, 91 were females, and in 25 cases sex was not reported. Ages ranged from 6 to 17 years (median 11.0 years). OROS methylphenidate HCl was indicated for ADHD (284), psychomotor hyperactivity (7), Autism (4), autism spectrum disorder (4), abnormal behaviour (3), disturbance in attention (2), oppositional defiant disorder (2), and 1 each for affective disorder, antisocial behaviour, Asperger's disorder, conduct disorder, irritability, learning disability, malaise, narcolepsy,

[116] 20121009968, 20121113519, 20121205184, 20130100066, 20130416235, 20130510777, 20130510780, 20130602295, 20130800481, 20130812504, 20130912835, 20131003970

[117] More than 1 indication was reported in some cases.

reactive attachment disorder of infancy or early childhood, and vision blurred. In 152 cases the indication was not specified. A total of 220 cases reported more than 1 event.

The frequency of PTs reported in these 449 cases is presented in Table 34.

Table 34 PTs Reported in OROS MPH Paediatric Patients 6 to 17 Years of Age

MedDRA PT	Number of Events (Cases)[a]
Decreased appetite	30
Drug ineffective	23
Nausea	19
Weight decreased	19
Headache	17
Insomnia	16
Aggression	15
Alopecia	15
Drug dose omission	14
Abnormal behaviour	13
Depression	12
Tic	12
Anxiety	11
Tachycardia	11
Vomiting	11
Incorrect dose administered	9
Off label use	9
Overdose	9
Treatment noncompliance	9
Drug effect decreased	8
Hallucination	8
Restlessness	8
Suicide attempt	8
Fatigue	7
Growth retardation	7
Medication error	7
Rash	7
Somnolence	7
Therapeutic response decreased	7
Tremor	7
Agitation	6
Disturbance in attention	6
Dyskinesia	6
Epistaxis	6
Irritability	6
Malaise	6
Mydriasis	6
Palpitations	6
Pruritus	6
Pyrexia	6
Raynaud's phenomenon	6
Wrong technique in drug usage process	6
Accommodation disorder	5
Convulsion	5
Depressed mood	5
Diarrhoea	5
Drug diversion	5
Drug prescribing error	5

Table 34 PTs Reported in OROS MPH Paediatric Patients 6 to 17 Years of Age

MedDRA PT	Number of Events (Cases)[a]
Feeling abnormal	5
Neutropenia	5
Psychotic disorder	5
Vision blurred	5
Weight increased	5
Abdominal pain	4
Adverse event	4
Capillary nail refill test abnormal	4
Chest pain	4
Crying	4
Diplopia	4
Dizziness	4
Hypertension	4
Medication residue present	4
Pain	4
Peripheral coldness	4
Prescribed overdose	4
Sinus bradycardia	4
Skin discolouration	4
Suicidal ideation	4
Weight gain poor	4
Abdominal pain upper	3
Accidental exposure to product	3
Arthralgia	3
Cold sweat	3
Epilepsy	3
Erythema	3
Eye pruritus	3
Hallucination, visual	3
Hallucinations, mixed	3
Heart rate increased	3
Hypersensitivity	3
Initial insomnia	3
Logorrhoea	3
Muscle spasms	3
Myalgia	3
Sleep disorder	3
Social avoidant behaviour	3
Syncope	3
Visual impairment	3
Activated partial thromboplastin time prolonged	2
Anger	2
Angioedema	2
Blister	2
Blood bilirubin increased	2
Blood pressure increased	2
Bundle branch block right	2
Chest discomfort	2
Confusional state	2
Constipation	2
Contusion	2
Cyanosis	2
Dark circles under eyes	2

Table 34 PTs Reported in OROS MPH Paediatric Patients 6 to 17 Years of Age

MedDRA PT	Number of Events (Cases)[a]
Delusion	2
Disturbance in social behaviour	2
Drug effect incomplete	2
Drug interaction	2
Dysphagia	2
Dysphonia	2
Dysphoria	2
Dyspnoea	2
Failure to thrive	2
Fear	2
Gynaecomastia	2
Haematuria	2
Hallucination, auditory	2
Hepatic function abnormal	2
Hot flush	2
Hypersomnia	2
Inappropriate schedule of drug administration	2
Intentional overdose	2
Joint swelling	2
Localised oedema	2
Mood altered	2
Muscle twitching	2
Nasopharyngitis	2
Ocular hyperaemia	2
Ocular icterus	2
Pain in extremity	2
Pallor	2
Paraesthesia	2
Personality change	2
Phobia	2
Pollakiuria	2
Poor quality drug administered	2
Restless legs syndrome	2
Sensory disturbance	2
Skin exfoliation	2
Strabismus	2
Substance abuse	2
Supraventricular tachycardia	2
Swollen tongue	2
Tachycardia paroxysmal	2
Therapeutic response unexpected	2

Table 34 PTs Reported in OROS MPH Paediatric Patients 6 to 17 Years of Age

MedDRA PT	Number of Events (Cases)[a]
Thrombocytopenia	2
Tongue spasm	2
Transaminases increased	2
Urinary retention	2
All other events singly reported[b]	201
Total	**920 (449)**

Key: MedDRA=Medical Dictionary for Regulatory Activities, MPH= Methylphenidate hydrochloride, PT= Preferred term

a: Cases may report more than 1 PT

b: Abasia, Abdominal discomfort, Abdominal distension, Abnormal faeces, Accidental overdose, Acute myocardial infarction, Adverse drug reaction, Alanine aminotransferase increased, Amenorrhoea, Amphetamines negative, Anaphylactic reaction, Apathy, Aphthous stomatitis, Arteritis, Arthropathy, Aspartate aminotransferase increased, Asperger's disorder, Asthenia, Atrioventricular block, Attention deficit/hyperactivity disorder, Back pain, Balance disorder, Benign hepatic neoplasm, Blood alkaline phosphatase increased, Blood copper increased, Blood creatinine increased, Blood glucose fluctuation, Blood thyroid stimulating hormone increased, Blood thyroid stimulating hormone increased, Blood triglycerides increased, Blood uric acid increased, Blood urine present, Blunted affect, Body height increased, Breast enlargement, Cardiac arrest, Cerebral vasoconstriction, Childhood psychosis, Chills, Collagen disorder, Complex regional pain syndrome, Concussion, Congestive cardiomyopathy, Conjunctivitis, Contraindication to medical treatment, Coprolalia, Coronary artery stenosis, Cyst, Cystic fibrosis, Delusional disorder, persecutory type, Dental care, Dependent personality disorder, Dermatitis atopic, Dermatosis, Distractibility, Drug administration error, Drug dependence, Drug dispensing error, Drug effect prolonged, Drug level increased, Drug screen negative, Drug tolerance, Drug withdrawal syndrome, Dry eye, Dysgeusia, Dysmenorrhoea, Dysphemia, Dystonia, Dysuria, Early menarche, Eating disorder, Ejection fraction decreased, Electrocardiogram abnormal, Electrocardiogram t wave inversion, Emotional disorder, Energy increased, Erectile dysfunction, Eructation, Exophthalmos, Extrapyramidal disorder, Extrasystoles, Eye disorder, Eye irritation, Eye pain, Eyelid oedema, Face oedema, Faecal incontinence, Faeces discoloured, Feeling cold, Feeling hot, Fracture, Gait disturbance, Gamma-glutamyltransferase increased, Gastrointestinal disorder, Gastrooesophageal reflux disease, Gilbert's syndrome, Glossodynia, Haemangioma, Haematoma, Head discomfort, Heat stroke, Helminthic infection, Hepatic enzyme increased, Hepatotoxicity, Hyperbilirubinaemia, Hyperglycaemia, Hyperhidrosis, Hypertransaminasaemia, Hyperventilation, Hypervigilance, Hypoaesthesia, Hypoaesthesia oral, Hypoglycaemia, Hypothermia, Hypovitaminosis, Ileus, Implantable defibrillator insertion, Incoherent, Incorrect dosage administered, Increased appetite, Influenza, Intention tremor, Intentional self-injury, Intracardiac thrombus, Jaundice, Laryngitis, Lethargy, Leukopenia, Libido increased, Lip oedema, Loss of consciousness, Madarosis, Memory impairment, Menstrual disorder, Menstruation irregular, Micturition urgency, Middle insomnia, Migraine, Mood swings, Motion sickness, Movement disorder, Muscular weakness, Myopathy, Nasal discomfort, Nephrotic syndrome, Neuropathy peripheral, Night sweats, Ocular hypertension, Oedema peripheral, Paradoxical drug reaction, Parosmia, Persecutory delusion, Photophobia, Pigmentation disorder, Poisoning deliberate, Polyuria, Poor personal hygiene, Precocious puberty, Prerenal failure, Priapism, Product coating issue, Product colour issue,

Table 34 PTs Reported in OROS MPH Paediatric Patients 6 to 17 Years of Age

MedDRA PT	Number of Events (Cases)[a]
Product quality issue, Psychomotor hyperactivity, Rash erythematous, Rash papular, Rash pruritic, Rebound effect, Respiratory distress, Rhabdomyolysis, Road traffic accident, Salivary hypersecretion, Scab, Scoliosis, Sedation, Self injurious behaviour, Self-medication, Sensation of foreign body, Serum sickness, Skin disorder, Skin reaction, Sleep apnoea syndrome, Speech disorder, Staring, Tearfulness, Therapeutic response delayed, Thinking abnormal, Thrombocytosis, Tinnitus, Tongue injury, Torticollis, Trismus, Tubulointerstitial nephritis, Urethral stenosis, Urine amphetamine negative, Urticaria, Vaginal discharge, Ventricular fibrillation, Ventricular hypokinesia, Vestibular neuronitis, Vitiligo	

Of the 77 cases reporting no age but an age category of infant, child or adolescent, 29 were males, 19 were females, and in 29 cases sex was not reported. OROS methylphenidate HCl was indicated for ADHD (28), Asperger's disorder (3), and 1 each for autism spectrum disorder and mental disorder. In 44 cases the indication was not specified. Thirty-one cases reported more than 1 event.

The frequency of PTs reported in these 77 cases is presented in Table 35.

Table 35 PTs Reported in OROS MPH Patients With Age Category of Infant, Child, and Adolescent

MedDRA PT	Number of Events (Cases)[a]
Drug ineffective	11
Off label use	6
Decreased appetite	5
Wrong technique in drug usage process	5
Depression	4
Alopecia	3
Feeling abnormal	3
Stereotypy	3
Weight decreased	3
Abnormal behaviour	2
Drug dose omission	2
Drug prescribing error	2
Dry eye	2
Liver function test abnormal	2
Medication residue present	2
Overdose	2
Red cell distribution width increased	2
Visual acuity reduced	2
Visual impairment	2
All other events singly reported[b]	64
Total	**127 (77)**

Key: MedDRA=Medical Dictionary for Regulatory Activity, MPH= Methylphenidate hydrochloride, PT= Preferred term

a: Cases may report more than 1 PT

b: Abdominal pain, Accommodation disorder, Acetonaemia, Aggression, Agitation, Anxiety, Aptyalism, Blood creatine phosphokinase increased, Blood pressure increased, Breath odour, Cough, Crying, Dental caries, Dizziness, Drug abuse, Drug effect decreased, Drug interaction, Drug name confusion, Dyshidrotic eczema, Dysphoria, Educational problem, Emotional disorder, Epistaxis, Feeling hot, Growth retardation, Haemoglobin decreased, Hepatic enzyme increased, Hyperkinesia, Hypersensitivity, Hypotension, Impulsive behaviour, Incorrect dose administered, Increased upper airway secretion, Insomnia, Intentional drug misuse, Lacrimation increased, Lethargy, Leukopenia, Lip discolouration, Logorrhoea, Malaise, Microcytosis, Muscle twitching, Nightmare, Ocular hyperaemia, Panic attack, Paraesthesia, Pharyngeal oedema, Phobia, Photosensitivity reaction, Prescribed overdose, Product packaging issue, Pruritus, Psychotic disorder, Restlessness, Skin discolouration, Sleep disorder, Suicidal ideation, Swelling face, Therapeutic response decreased, Therapy cessation, Vomiting, Weight gain poor, Weight increased

Conclusion

Based on the review of cases, no changes to the CCDS are warranted.

16.3.5.3. Effects of Long-Term Treatment

According to the Maintenance/Extended Treatment Section of the CCDS: "*The long-term use of methylphenidate has not been systematically evaluated in controlled trials. The physician who elects to use [OROS methylphenidate hydrochloride] for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug. The physician who elects to use [OROS methylphenidate HCl] for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy"* and in the Warning and Precautions Section: *"although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted "*and "*Periodic hematologic monitoring (Complete Blood Count, differential, and platelet counts) is advised during prolonged therapy.*"

Methods

The GMS safety database was searched for medically confirmed cases during the report period involving OROS methylphenidate HCl use where the treatment start and stop dates or treatment duration were identified as ≥365 days, and a search where the treatment stop and start dates or treatment duration was ≥730 days. [118,119]

Results

A total of 40 cases (see Appendix 7.3 for AER numbers) were identified by the above searches. All cases were medically reviewed and 6 cases were selected for presentation due to potential medical significance.

Patients <18-years-old

- [redacted] (***Thrombocytopenia, Neutropenia, Leukopenia***): [redacted] with autism, challenging behaviour, conduct disorder, and moderate learning disability was treated with OROS methylphenidate HCl 54 mg/day initiated "over a year ago" in 2010 for ADHD. Concomitant medications were aripiprazole, melatonin, and valproate. On 22 October 2012, the patient's neutrophil count was 1.64, platelet count was 66, white blood cell (WBC) count was 3.9 (units and normal ranges not provided). The following month, his neutrophil count was 1.67, platelet count was 67, and WBC was 3.9 (units and normal ranges not provided). The patient was seen by a paediatrician to exclude any contributing physical disorders and advised that OROS methylphenidate HCl should be withdrawn. Eight days after treatment was withdrawn, neutrophil count was 3.15, platelet count was 112 and WBC was 5.1 (units and normal ranges not provided). Thirty-seven days after OROS methylphenidate HCl was withdrawn, the patient recovered from the events, and his

[118] SDE00028837 OROS ®methylphenidate HCL PBRER/PSUR (11 October 2012 to 31 October 2013) Aggregate dataset query

[119] For purposes of the search, if only the year of a date was provided, the date was defaulted to the first of the year and if only month and year were provided for a date, the date was defaulted to the first day of the month.

counts had returned to normal: neutrophil count was 2.95, and platelets were 262 (units and normal ranges not provided). Refer to Section 16.3.5.2.4, Use in Children.

- [redacted] **(*Growth retardation*, Wrong technique in drug usage process)**: A [redacted] was treated with OROS methylphenidate HCl 18 mg/day for ADHD. Co-suspect medication was non-company methylphenidate HCl (characterizing wrong technique in drug usage process). Since 4 years after the start of both of the drugs, the patient experienced growth retardation. Both of the patient's parents were noted to be tall with a height of more than 180 centimetres. OROS methylphenidate HCl and methylphenidate HCl were withdrawn after 5 years of treatment and the patient had not recovered from growth retardation (refer to Section 16.3.5.2.4, Use in Children).
- [redacted] **(*Growth retardation*, Drug ineffective)**: [redacted] was treated with OROS methylphenidate HCl 18 mg for ADHD. Approximately 1 year after the initiation of treatment, it was reported that the patient had not grown in height at all during the past year. Treatment was temporarily stopped for 3 months for an unspecified reason. Approximately 1 year later, it was reported that the patient's height had increased by 1.4 cm; his height curve had been steady and had dropped slightly since OROS methylphenidate HCl was initiated, but was levelled out. The patient was reported to have a normal appetite and was eating well. The action taken with OROS methylphenidate HCl was not reported and the event was resolving (refer to Section 16.3.5.2.4, Use in Children).
- [redacted] **(*Palpitations, Supraventricular tachycardia*)**: [redacted] was treated with OROS methylphenidate HCl 36 mg/day for ADHD for 18 months, which was then increased to 54 mg/day. Concomitant medications were not reported. After an unspecified time, the patient experienced palpitations and supraventricular tachycardia, with a blood pressure of 150mmHg and heart rate 150/minute (normal ranges not provided). The dose of OROS methylphenidate HCl was unchanged and the patient recovered from the events (refer to Section 16.3.5.2.4, Use in Children).

Patients ≥18-years-old

- [redacted] **(*Myocardial infarction*)**: [redacted] with a reported healthy cardiac and pulmonary history was treated with OROS methylphenidate HCl 36 mg/day for concentration disorder. Concomitant medication was unspecified contraceptives. Approximately 3 years after the initiation of OROS methylphenidate HCl, the patient was hospitalised due to chest pain and a cramp-like feeling in her arm. Her ECG revealed a reaction on ST-waves inferior and a right electrical axis deviation. Initial troponin T (TnT) level was 30 (units and normal range not provided). Further TnT leakage occurred with a maximum level of 76.8 (units not reported, reference value for myocardial infarction [MI] 15 ng/L). The patient was investigated without any findings of cause of the event and it was evaluated as a probable cardio-toxic effect of OROS methylphenidate HCl despite the fact that the patient had been treated for a long time. OROS methylphenidate HCl was withdrawn and the patient recovered (see Section 16.3.6.1, Ischaemic Cardiac Events).
- [redacted] **(*Palpitations, Anxiety, Depression*, Insomnia, Arthralgia, Pain, Multiple allergies, Pain of skin)**: [redacted] was treated with OROS methylphenidate HCl 36 mg/day, initiated "12 months ago in 2012." On an unspecified date, the patient experienced palpitations and insomnia. Her ECG was normal. The patient also experienced Pain of skin when touched. OROS methylphenidate HCl was withdrawn because the patient had developed arthralgia and generalised pain and the patient's mother reported that the

patient was developing allergies. Following the withdrawal of OROS methylphenidate HCl, the patient experienced anxiety and depression. The outcome of all of the events was not reported.

Discussion

Of the 6 cases selected for presentation, [redacted]) reported the serious unlisted event of Growth retardation in children. Case 20131015631 reported that OROS methylphenidate HCl was withdrawn after 5 years of treatment and the event had not resolved. This case was confounded by the simultaneous use of methylphenidate HCl. Case [redacted] reported that the patient's height curve had dropped slightly since OROS methylphenidate HCl was started, but the event was resolving and the action taken with OROS methylphenidate HCl was not reported, precluding further assessment.

[redacted] reported serious listed events of thrombocytopenia and leukopenia, and a serious unlisted event of neutropenia after approximately 2 years of treatment with OROS methylphenidate HCl. Although the patient's blood levels did normalise after OROS methylphenidate HCl was withdrawn, this case was confounded by concomitant medications aripiprazole[120], melatonin[121] and valproate[122], all of which have reported hematologic adverse reactions in post-marketing or clinical settings (leukopenia, neutropenia, thrombocytopenia; leukopenia and thrombocytopenia; and thrombocytopenia, leukopenia and pancytopenia; respectively). As noted in the CCDS, periodic hematologic monitoring is recommended during prolonged treatment.

The remaining [redacted]) all reported cardiovascular events. [redacted] reported an MI [redacted] with no prior reported cardiac history after approximately 3 years of treatment with OROS methylphenidate HCl. The patient was taking an unspecified contraceptive, but no further information was provided if this was a hormonal contraceptive, which are associated with an increased risk of MI.[1] [redacted] reported the serious listed events of palpitations and supraventricular tachycardia in a [redacted] Treatment with OROS methylphenidate HCl was continued unchanged, and the patient recovered. The patient was reported to have received OROS methylphenidate HCl for 18 months and then had a dosage increase, but the actual latency to the event was not reported.

[120] ABILIFY® Summary of Product Characteristics: http://www medicines.org.uk/emc/medicine/20802/SPC/Abilify+7.5+mg+ml+solution+for+injection+ (intramuscular)/#UNDESIRABLE_EFFECTS. Accessed 19 November 2013

[121] CIRCADIN®Summary of Product Characteristics: http://www medicines.org.uk/emc/medicine/25643/SPC/Circadin/#UNDESIRABLE_EFFECTS. Accessed on 19 November 2013

[122] DEPAKOTE®Summary of Product Characteristicsicst: http://www.medicines.org.uk/emc/medicine/25929/SPC/Depakote+250mg+Tablets/# UNDESIRABLE_EFFECTS. Accessed 19 November 2013

[123] Contraceptives, progestin, in MICROMEDEX2.0®: http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ ND_PR/ evidencexpert/CS/3BC451/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/ 36E7C6/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/ evidencexpert.IntermediateToDocumentLink?docId=1462&contentSetId=31&title=Contraceptives%2C+Progestin&servicesTitle=Contraceptives%2C+Progestin. Accessed 20 November 2013

[redacted] reported a serious listed event of palpitations with a normal ECG, and additionally reported other serious listed and nonserious unlisted events. The latency to the events was not reported but the patient was stated to have been on OROS methylphenidate HCl treatment for 1 year. The event outcomes were not reported after the withdrawal of treatment.

The MAH agreed to monitor the long-term study undertaken by the ADDUCE and funded under the EU seventh framework programme. It is anticipated that this will provide independent information on the long-term use of methylphenidate in European ADHD patients. The MAH also agrees to continue to screen for new publications on long-term safety study results, as well as, to monitor on-going external research efforts related to long-term use of OROS methylphenidate HCl.

Conclusion

Review of the cases does not indicate any new signals or trends. No changes to the CCDs are warranted at this time.

16.3.6. Summary of Other Risks

16.3.6.1. Cardiac Disorders: Ischaemic Cardiac Events

Introduction

Events in this SOC were reviewed due to potential medical significance. According to the RMP, Arrhythmias, Cyanosis, Ischaemic cardiac events, QT prolongation, and Sudden death are potential risks associated with the use of methylphenidate HCl. Hypertension and Tachycardia are RMP identified risks associated with the use of methylphenidate containing products.

According to the CCDS Warning and Precautions Section: *"Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities." and "…caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. [Blood pressure (especially for patients with hypertension) and heart rate should be monitored at appropriate intervals in patients taking [OROS methylphenidate HCl]."*

The following events are listed in the CCDS: Angina pectoris, Blood pressure increased, Bradycardia, Cardiac murmur, Chest discomfort, Chest pain, Extrasystoles, Heart rate increased, Hypertension, Palpitations, Raynaud's phenomenon, Supraventricular tachycardia, Tachycardia, and Ventricular extrasystoles.

As part of a commitment detailed in the RMP for OROS methylphenidate HCl, the MAH continues to perform enhanced pharmacovigilance in the form of a targeted questionnaire to all reporters of sudden death.

The following MedDRA SMQs were selected to identify cases for review: Myocardial Infarction SMQ (Narrow), and Other Ischaemic Heart Disease SMQ (Narrow).

Results

The search described above identified 9 cases[124] (8 initial, 1 follow-up). The follow-up case ([redacted] involved multiple, unidentifiable patients; the information received in the follow-up report related to the incidence of sudden death/ventricular arrhythmia in 43,999 OROS methylphenidate HCl users compared to 415,406 nonusers reporting a ratio of 2.08 (1.50-2.88). This case is excluded from further review. There were an additional 3 initial cases from literature ([redacted] which also involved multiple, unidentifiable patients. [redacted] reported the PT Myocardial infarction and concerned a meta-analysis of various publications involving methylphenidate treatment; [redacted] reporting the PT Angina pectoris, concerned the use of methylphenidate in the treatment of symptomatic handling of oncology patients, and [redacted] reporting the PTs Myocardial infarction and Angina pectoris, involved an analysis of cardiac events experienced in a cohort of 30,576 paediatric patients and young adult patients (aged between 3 and 20 years). The limited information relating to patient demographics, medical history, treatment dosage, latency and/or details regarding the events precludes adequate medical assessment; therefore, these cases are not included for further review.

Table 36 displays a count of the selected PTs, all of which were serious, by age in the 5 remaining cases[128] (all spontaneous reports) received for the current PSUR reporting period.

Table 36: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Ischaemic Cardiac Events

Preferred Term	Number of Events[a]	
Age (years)	**<18[b]**	**≥18[c]**
Acute myocardial infarction	1	-
Coronary artery stenosis	1	-
Myocardial infarction	-	4
Subtotal	**2**	**4**
Total	**6**	

Key: MPH= Methylphenidate hydrochloride; PT= Preferred term
a: Dash (-) indicates the specified PT was not identified within the age/age group
b: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
c: Includes patients ≥18-years-old and/or patient age category: adult, elderly.

Of the 5 cases included for further review, 4 involved adult patients. Of these, 2 cases provided limited information: case (20130409619), involved an adult male who experienced a myocardial infarction (MI) and provided limited information regarding the patient's history, concomitant

[redacted], [redacted]

[125] Schelleman H, Biler WB, Kimmel SE, et al. Pharmacoepidemiology and Drug Safety 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management Chicago, IL United States. Conference Start: 20110814 Conference End: 20110817 2011: 20: S122.

[126] Papa MP. Use of methylphenidate in patients with advanced cancer. *Revista Medica del Uruguay*. 2013; 29 (1): 58-63.

[127] Winterstein AG, Gerhard T, Shuster J, Saidi A. Cardiac Safety of methylphenidate versus amphetamine salts in the treatment of ADHD. *Pediatrics*. 2009;124 (1):e75-80.

[redacted]

medications, latency of onset, course of events, action taken, and outcome. It was also reported that the medication was probably non-Company methylphenidate HCl. [redacted] involved [redacted] of smoking and "pre-infarction" 8 years ago after giving birth. The patient received OROS methylphenidate HCl 72mg/day in 2 doses, a 54 mg morning dose and a 18 mg afternoon dose for ADHD. Concomitant medications included topiramate, aripiprazole, duloxetine, propiomazine and zopiclone. The patient experienced an MI 2 to 3 years after starting OROS methylphenidate HCl and was hospitalized. OROS methylphenidate HCl was withdrawn and the patient underwent a percutaneous coronary intervention. After discharge the patient requested to restart OROS methylphenidate HCl as she experienced withdrawal symptoms. The outcome was not reported.

The remaining 3 cases involving 2 adults, and 1 paediatric patient, are presented further below.

Patients <18-years-old

- [redacted] (***Acute myocardial infarction*, Intracardiac thrombus, Ventricular hypokinesia, Implantable defibrillator insertion, *Coronary artery stenosis, Ventricular fibrillation, Ejection fraction decreased***): [redacted] with OROS methylphenidate HCl, 54 mg for ADHD. Concomitant medications were not administered to the patient. "Months or years" after starting OROS methylphenidate HCl, the patient experienced sudden ventricular fibrillation during physical activity. The patient was resuscitated with DC conversion ("amongst other things") and was subsequently cooled and transferred to a hospital where several investigations on the same day showed a large lateral/posterior acute MI, a blood clot in the heart, and electrical instability but normal open coronary arteries. It was suspected that there was transient occlusion of the ramus circumflexus artery. On an unspecified date, the patient was diagnosed with reduced left ventricular function with ejection fraction of 45% with lateral-posterior hypoakinesia. The patient had normal blood lipids and no familial disposition. On an unspecified date, the patient had an implantable cardioverter defibrillator (ICD) pacemaker implanted. The patient had undergone ECG, blood tests, MRI, CT electrophysiological study, and coronary angiography. Fifteen days after the onset of the event, OROS methylphenidate HCl was withdrawn. The patient recovered from the MI and cardiac thrombus with sequelae (see Section 16.3.5.2.4, Use in Children).

Patients ≥18-years-old

- [redacted] (***Myocardial infarction*): [redacted] with normal pulmonary and cardiac condition was treated with OROS methylphenidate HCl, 36 mg once a day for concentration disorder. Concomitant medications included unspecified contraceptives. Approximately 4 to 5 years after starting OROS methylphenidate HCl, the patient was hospitalised due to episodes of chest pain and a cramp-like feeling in her left arm. An ECG revealed a reaction on ST-waves inferior and a right electrical axis deviation. The initial level of TnT was 30 (unspecified units). Further TnT leakage occurred with a maximum level of 76.8 (reference value for myocardial infarction 15 ng/L). The patient was investigated with ultrasonic cardiography, coronary angiography, and magnetic X-ray of the heart without finding any cause for the patient's problems. The patient denied having any infection in the last couple of months. The event was evaluated as probable cardio-toxic effect of OROS methylphenidate HCl despite the fact that the patient had been treated for a

long period of time. OROS methylphenidate HCl was withdrawn and the patient recovered (see Section 16.3.5.3, Effects of Long-Term Treatment).

- [redacted] (***Myocardial infarction***): [redacted] was treated with OROS methylphenidate HCl for ADHD. Co-suspect drugs included non-Company methylphenidate hydrochloride and zolpidem. For several months the patient had a sensation of weight in his chest with physical activity; 2 days after the dose of OROS methylphenidate HCl was increased to 54 mg a day (26 days after initiation), he experienced strong chest pain lasting about 30 minutes. On an unspecified date, the patient received emergency care after a period of stronger chest pain. An MI was diagnosed with troponin results (not provided). Coronary angiography revealed a small plaque in the mid left anterior descending artery with significant stenosis. An echocardiogram revealed normal systolic function. The patient received treatment with a drug-eluting stent. Action taken with OROS methylphenidate HCl, methylphenidate HCl, and zolpidem was not reported. The patient recovered from the event.

Discussion

Patients <18-years-old

There was 1 case ([redacted] received during the review period involving a paediatric patient who experienced an ischaemic cardiac event (acute MI with coronary artery stenosis). The most likely etiology of the acute MI in this patient was the cardiac thrombus and per the reporter, "Investigation for paradox embolism/coagulopathy/coronary spasm was ongoing" in an attempt to determine the cause of thrombus formation in this previously healthy 11-year-old (refer to Section 16.3.5.2.4, Use in Children).

Patients ≥18-years-old

Of the 4 cases involving adult patients (all reporting MI), 1 provided minimal information thereby precluding medical assessment. [redacted] was confounded by the patient's history of pre-infarction and smoking, which is a risk factor for developing atherosclerosis and subsequent myocardial infarction.[129] Use of OROS methylphenidate HCl in patients with pre-existing structural cardiac abnormalities is contraindicated according to the CCDS.

Of the 2 remaining cases, 1 reported concomitant use of contraceptive medication (unspecified) and the reporter did not take into account the small but increased risk of vascular disorders, including MIs and pulmonary embolism, in patients on oral contraceptives. The patient is reported to have had a normal cardiac history, however, it is not reported if the patient was a smoker, an additional risk factor for cardiac disease. A direct toxic effect of OROS methylphenidate HCl on the heart seems an unlikely cause of the patient's symptoms as she was receiving a low dose of OROS methylphenidate HCl for a number of years without incident. In addition, the patient described acute symptoms which are not consistent with the effect of years of exposure to a cardio-toxic drug. [redacted]

[129] Myocardial infarction : http://emedicine medscape.com/article/155919-overview#aw2aab6b2b4. Accessed 18 November 2013.

patient diagnosed with an MI secondary to a small plaque in the mid left anterior descending artery with significant stenosis.

Conclusion

Review of these cases does not provide evidence that represent a new safety concern. No changes to the CCDS or RMP are warranted at this time.

16.3.7. Psychiatric Disorders

16.3.7.1. Psychosis and Other Psychiatric Disorders

Introduction

Psychosis/mania and hallucinations (auditory, skin sensation, visual disturbance) are RMP identified risks with the use of methylphenidate containing products. In the Adverse Reaction Section of the CCDS, Hallucination, Hallucination auditory, Hallucination visual, and Mania are listed as very rare ADRs during post-marketing experience and the CCDS Warning and Precautions Section states: "*Psychotic (e.g., hallucinations) or manic symptoms have been reported in patients without a prior history of psychotic illness or mania during treatment with [OROS methylphenidate HCl] at usual dosages,"* and if such symptoms occur *"consideration should be given to a possible causal role of [OROS methylphenidate HCl] and discontinuation may be appropriate.*"

The following MedDRA SMQ was selected to identify cases for review: Psychosis and Psychotic Disorders (Broad). In addition, the following MedDRA PTs were selected to identify cases for review due to potential medical significance: Euphoric mood and Bruxism.

Results

The search described above identified 88 medically confirmed cases (77 initial, 11 follow-up), see Appendix 7.3 for AER numbers. Of the medically confirmed cases, a review of the follow-up cases did not change the prior assessment of the event in 6 cases[130]; these cases are, therefore, not discussed further. The 5 remaining follow-up cases [redacted] contained new information related to a topic of interest, therefore these cases are included for analysis: [redacted] (negative rechallenge with methylphenidate), [redacted] (reporter updated the causality of the events of interest from highly probable to not related), [redacted] (medical history updated to include depression and conduct disorder/oppositional defiant disorder and updated the causality assessment of the events of interest to not related), [redacted] reporter [redacted] were no cases received for this topic which reported an age less than 6-years-old or greater [redacted] 65-years-old.

[130] 20110307513, 20120306357, 20120900530, 20120904103, 20121002370, 20121001042

Table 37: Counts of Select PTs by Age and Seriousness in Cases With OROS MPH: Psychosis and Other Psychiatric Disorders (n=82)

Preferred Term	Number of Events[a,b,c,d]		
Age (years)	**6-17[e]**	**18-65[f]**	**NR[g]**
Abnormal behaviour	4 (11)	-	-(7)
Apathy	-(1)	-(1)	-
Blunted affect	-(1)	-	-
Bruxism	-	-(1)	-(2)
Childhood psychosis	1	-	-
Delusion	2	3	-
Delusional disorder, persecutory type	1	-	-
Euphoric mood	-(1)	-	-
Flat affect	-	-(1)	-
Hallucination	7	3	4(1)
Hallucination, auditory	1(1)	1	-
Hallucination, visual	5	-	-
Hallucinations, mixed	3	-	-
Hallucination, tactile	-	1	1
Incoherent	1	-	-
Logorrhoea	2(2)	-	-(2)
Major depression	-	-	1
Paranoia	-	1	1
Persecutory delusion	1	-	-
Psychotic disorder	7	3	2 (1)
Social avoidant behaviour	-(4)	1	-(5)
Speech disorder	1	-	-
Thinking abnormal	-(1)	-	-(2)
Subtotal	36(22)	13(3)	9(20)
Total[h]	**103**		

Key: MPH=Methylphenidate hydrochloride; n=number, NR=Not reported, PT=Preferred term

a: Cases may have reported more than 1 event of interest
b: Events reported from medically confirmed cases
c: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified
d: Dash (-) indicates the specified PT was not identified within the age/age group
e: Includes patient age category: neonate, infant, adolescent, child.
f: Includes patient age category: adult
g: Includes patients with no reported age and age category.
h: Includes serious and nonserious events.

Nine[131] of the 82 cases for analysis reported non-serious listed events of interest: Logorrhoea (4 cases), Bruxism (3 cases), and 1 case each of Hallucination and Hallucination, auditory.

Twenty-eight cases (see Appendix 7.3) reported 31 serious listed events of interest: Hallucination (10 cases), Psychotic disorder (9 cases), Hallucination, visual (4 cases), Abnormal behaviour (2 cases), Hallucinations, mixed (2 cases), and 1 case each of Childhood psychosis, Hallucination, auditory, Logorrhoea, and Major depression. Two of these cases [redacted] additionally reported a nonserious listed event of Abnormal behaviour.

[redacted]

Table 38, Table 39 and Table 40 present an overview of the remaining 45 cases (see Appendix 7.3) reporting unlisted Psychiatric Disorder events presented by age/age group.

Table 38: Characteristics for OROS MPH Cases Reporting Psychosis and Other Psychiatric Disorders in Patients 6 to 17-years-old or Age Category Neonate, Infant, Child or Adolescent (n=24)

Characteristic		Number of Cases
Source	Spontaneous	22
	Literature	2
Patient Sex	Male	19
	Female	4
	Not reported	1
Patient Age (Years)[a]	0-5	0
	6-13	16
Mean: 10.35	14-17	4
Median: 9.5	Child	3
	Adolescent	1
Daily Dose at Onset of Adverse Event	18 mg/day	2
	18 mg twice a day	1
	27 mg/day	3
	36 mg/day	2
	54 mg/day	2
	810 mg[b]	1
	Not reported	13
Indication[c]	ADHD	13
	Unspecified indication	8
	Psychomotor hyperactivity	2
	Conduct disorder	1
	Malaise	1
Outcome of Event of Interest[d]	Not reported	14
	Recovered/Resolved	9
	Not Recovered/Not Resolved	4

Key: ADHD=Attention Deficit Hyperactivity Disorder, mg=milligrams, MPH=Methylphenidate hydrochloride, n=Number

a: Patient age category provided for cases with no age reported
b: Dosage reported in a suicide attempt
c: Cases may report more than 1 indication
d: Cases may report more than 1 event of interest

Table 39: Characteristics for OROS MPH Cases Reporting Psychosis and Other Psychiatric Disorders in Patients 18 to 65 years-old (n=7)

Characteristic		Number of Cases
Source	Spontaneous	5
	Clinical	1
	Literature	1
Patient Sex	Male	3
	Female	3
	Not reported	1
Patient Age (Years)[a]	18-35	4
	Adult	3
Mean: 24 **Median: 25.5**		
Daily Dose at Onset of Adverse Event	18 mg/day	1
	10 mg twice a day	1
	36 mg/day	1
	63 mg/day	1
	Not reported	3
Indication	ADHD	5
	Unspecified indication	2
Outcome of Event of Interest[b]	Recovering/Resolving	4
	Not reported	3
	Recovered/Resolved	2

Key: ADHD=Attention Deficit Hyperactivity Disorder, mg=milligrams, MPH=Methylphenidate hydrochloride, n=Number
a: Age group is provided for cases with no age reported
b: Cases may report more than 1 event of interest

Table 40: Characteristics for OROS MPH Cases Reporting Psychosis and Other Psychiatric Disorders in Patients With No Reported Age/Age Category (n=14)

Characteristic		Number of Cases
Source	Literature	7
	Spontaneous	6
	Clinical	1
Patient Sex	Not reported	11
	Male	2
	Female	1
Daily Dose at Onset of Adverse Event	27 mg/day	2
	54 mg/day	1
	Not reported	11
Indication	ADHD	9
	Unspecified indication	5
Event Outcome	Not reported	14

Key: ADHD=Attention Deficit Hyperactivity Disorder, mg= milligrams. MPH=Methylphenidate hydrochloride, n=Number

Twenty-nine of these cases (see Appendix 7.3) reported 33 non-serious unlisted events of interest: Abnormal behaviour (16 cases), Social avoidant behaviour (9 cases), Thinking abnormal (3 cases), Apathy (2 cases), and 1 case each of Blunted affect, Euphoric mood, and Flat affect.

The remaining 16 cases[132] (9 patients [6 to 17-years-old], 5 patients [18 to 65-year-old], and 2 cases [no reported age or age group]) reported serious unlisted Psychosis and Other Psychiatric Disorder events and are listed below by age categories.

Patients 6 to 17-years-old

Follow-up information in case [redacted] reported that the patient had concurrent conditions of depression and conduct disorder/oppositional disorder. Risperidone was updated from a co-suspect to a concomitant medication and it was reported that the patient was not using his drugs regularly during his suicide attempt and had symptoms of depression. OROS methylphenidate HCl was discontinued and the patient recovered from the event (see also Section 16.2.1.4, Depression and Suicide/Self Injury, Section 16.2.4, Experience with Overdose, Deliberate or Accidental and Its Treatment, and Section 16.3.5.2.4, Use in Children).

[redacted] involved an event of Speech disorder event related to a Tic the patient was experiencing (see Section 16.3.7.2, Tic and Tourette's disorder and Section 16.3.5.2.4, Use in Children). [redacted] reported events of Delusion and Psychotic disorder respectively (refer to Section 16.3.5.2.4, Use in Children). Both cases contained limited information regarding concomitant medications, medical history, latency and the specifics of the psychiatric event, while case [redacted] reported nonspecific abnormal behaviour in the context of a deliberate multiple drug overdose suicide attempt (see Section 16.2.4, Experience in Overdose, Deliberate and Accidental, and Its Treatment, Section 16.2.5.1, Depression and Suicide/Self Injury and Section 16.3.5.2.4, Use in Children). The 4 remaining cases are presented below:

- **2 [redacted] (*Hallucination visual, Delusional disorder persecutory type, Persecutory delusion*)**: [redacted] with nonspecific personality disorder and cyclothymic disorder was treated with OROS methylphenidate HCl 36 mg/day for hyperactive behaviour. Concomitant medications were not reported. Approximately 14 months after the initiation of OROS methylphenidate HCl, the patient experienced Hallucinations (visual), and delusions of persecution. OROS methylphenidate HCl was withdrawn and the patient recovered from the events (also reported as not recovered, see Section 16.3.5.2.4, Use in Children).
- **[redacted] (*Hallucinations mixed*, Convulsion, Dyspnoea, Aggression, Insomnia, Restlessness, *Logorrhoea, Incoherent*)**: [redacted] was treated with OROS methylphenidate HCl 27 mg for ADHD. The same day, after her first dose, the patient experienced Hallucinations (auditory and visual), and Logorrhoea. OROS methylphenidate HCl was withdrawn and the outcome of the events was not reported (see Section 16.3.5.2.4, Use in Children).

[redacted]

[133] Pringsheim T. Psychopharmacology for the Clinician. *J Psychiatry Neuroscience* 2012;37 (6):E11-E12

- [redacted] (***Delusion***): A [redacted] with OROS methylphenidate HCL 18 mg twice a day for an unspecified indication. Co-suspect drug was melatonin. Concomitant medication was budesonide. Approximately 2 months after the initiation of OROS methylphenidate HCl, the patient experienced a Delusion. OROS methylphenidate HCl was withdrawn, melatonin was unchanged and the patient recovered from the event (see Section 16.3.5.2.4, Use in Children).
- [redacted] (***Psychotic disorder, Hallucination***): [redacted] was treated with OROS methylphenidate HCL 18 mg/day for an unspecified indication. After "the patient used OROS methylphenidate HCL for the first time," he experienced Psychotic disorder and Hallucination. OROS methylphenidate HCL was withdrawn and the patient recovered from the events (see Section 16.3.5.2.4, Use in Children).

Patients 18 to 65-years-old

[redacted] involved [redacted] who took OROS methylphenidate HCl in combination with alcohol and experienced a delusion of being raped; causing her to file a false report (refer to Section 16.2.3, Drug Interaction). Spontaneous case [redacted] involved multiple adult patients of unspecified age and sex who were treated with OROS methylphenidate HCl, compulsively injected the drug intravenously (characterising Wrong route of drug administration), and experienced Social avoidant behaviour and Hallucinations among other events (see also Section 16.2.5.1, Drug Abuse/Misuse, and Section 16.2.5.2, Medication Error/Maladministration). The 3 remaining cases in this age group are presented below:

- [redacted] (***Psychotic disorder***): [redacted] was started on OROS methylphenidate HCl at 18 mg/day and then gradually increased to 63 mg/day. Follow-up information reported that approximately 6 months after the initiation of OROS methylphenidate HCl, and 10 days after the dosage was increased to 63 mg/day, the patient experienced Psychotic disorder (previously reported as Confusional state). It was considered that the event could have been induced by the patient's personality and that she was predisposed to psychosis due to stress. The investigator also considered that the causality between the psychotic disorder and OROS methylphenidate HCL was possible. OROS methylphenidate HCL was withdrawn and the patient was recovering from the event.
- [redacted] (***Paranoia,*** **Off label use**): [redacted] was treated with OROS methylphenidate HCl "10 mg" twice a day for an unspecified indication (characterised as Off label use). Concomitant medications were not reported. Eleven days after the initiation of OROS methylphenidate HCl, the patient experienced Paranoia. It was reported that the patient had been pre-warned about this as a possible side-effect and therefore stopped treatment immediately. The patient recovered from paranoia within 2 days (see Section 16.2.5.2, Medication Error/Maladministration).
- [redacted] (***Delusion, Hallucination tactile***, **Libido increased, Anger, Delusion, Affect lability,** ***Hallucination auditory***): [redacted] with a sleep disorder, history of childhood trauma, and a family history (mother) of bipolar disorder/suicide, was treated with OROS methylphenidate HCL 18 mg for ADHD. Concomitant medications included amitriptyline. Two weeks after the initiation of OROS methylphenidate HCL, the patient experienced Delusions and Hallucinations (tactile and auditory). She was reported to have fits of rage and felt "emotionally upside down." The patient related the events to her childhood trauma. OROS methylphenidate HCL was withdrawn and then restarted and the

patient was recovering from the events. The reporter considered the events not related to OROS methylphenidate HCL (see Section 16.2.1.4, Depression and Suicide/Self Injury and Section 16.3.8, Breast and Reproductive disorders).

Patients with no reported age/age category

[redacted] involved multiple patients of unspecified age and sex with a medical history of multiple addictions and drug abuse who used OROS methylphenidate HCl intravenously and experienced Paranoia and Hallucinations among other events (refer to Section 16.2.5, Drug Abuse/Misuse and Section 16.2.5.2, Medication Error/Maladministration). [redacted] involved a male patient who was treated with OROS methylphenidate HCl for an unspecified indication and "upon starting" OROS methylphenidate HCl, experienced Hallucination, tactile. The action taken with OROS methylphenidate HCl and the outcome of the event was not reported. No further information was provided.

Discussion

The Warnings & Precaution section of the CCDS states that *"Psychotic (including hallucinations) or manic symptoms have been reported in patients without a prior history of psychotic illness or mania during treatment with OROS methylphenidate HCl at usual dosages,"* and if such symptoms occur *"consideration should be given to a possible causal role of OROS methylphenidate HCl and discontinuation may be appropriate."* Additionally, clinical experience *"suggests that in psychotic patients, methylphenidate may exacerbate symptoms of behaviour disturbance and thought disorder."*

During the reporting period, there were 3 nonserious cases of the listed event bruxism and 1 case of nonserious unlisted Euphoric mood.

Of the 82 cases analysed which reported Psychiatric disorder events, 37 cases reported listed events, while 45 cases reported unlisted events. Of the 45 cases reporting unlisted events, 16 cases reporting serious unlisted events and 7 were further presented.

Patients 6 to 17-years-old

Of the 4 cases presented, [redacted] reported the onset of a psychotic disorder the same day OROS methylphenidate HCl was started. One patient recovered after OROS methylphenidate HCl was withdrawn, and the other patient's outcome was not reported. [redacted] reported the onset of hallucinations and delusions in a patient with a history of psychotic disorders and [redacted] reported the onset of delusions after 2 months of treatment with OROS methylphenidate HCl in a patient who was treated for an unspecified indication.

Patients 18 to 65-years-old

Of the 3 cases presented, 2 cases [redacted]) reported the onset of psychotic disorders 6 months and 2 weeks, respectively, in a patient reported to have a predisposition to psychosis and a patient with a history of childhood trauma and a family history of psychotic disorder. [redacted] also reported that the event occurred 10 days after the dose of OROS methylphenidate HCl was increased. [redacted] reported the onset of a psychotic disorder after 11 days of treatment with OROS methylphenidate HCl in a patient treated for an unspecified indication.

Patients with no reported age/age category

Of the 2 cases [redacted]) reporting serious unlisted events (Paranoia, Hallucinations and Hallucinations tactile, respectively), one involved multiple unspecified patients and one contained limited information.

Conclusion

The events in this review were consistent with the safety profile of OROS methylphenidate HCL. No changes are warranted to the CCDS or RMP.

16.3.7.2. Tic and Tourette's Syndrome

Introduction

Tics/Tourette's syndrome/Dystonia is an important potential risk with the use of OROS methylphenidate HCl in the RMP.

The Warnings and Special Precautions for Use of the CCDS states, "*CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics. Therefore, clinical evaluation for tics in patients should precede use of stimulant medication. Family history should be assessed.*" The CCDS also includes a contraindication for OROSmethylphenidate HCl therapy if the patient has a family history of or diagnosis of Tourette's disorder.

The following MedDRA SMQ was selected to identify cases for review: Dystonia (Broad). In addition, the following MedDRA PTs were selected to identify cases for review due to potential medical significance: Tic (contained in the Dystonia SMQ), and Tourette's disorder.

The MedDRA SMQ Dystonia (Broad) and the PTs Tic and Tourette's disorders were selected to identify cases for review. Tic is a listed event in the CCDS.

Results

The search described above identified 53 medically confirmed cases (48 initial, 5 follow-up), see Appendix 7.3 for AER numbers. Of the medically confirmed cases, a review of the follow-up

cases did not change the prior assessment of the event in all 5[134] cases; these cases are, therefore, not discussed further.

Table 41 displays a count of the selected PTs by age and seriousness in the remaining 48 cases included for analysis in the current PSUR reporting period.

Table 41: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Tics and Tourette's Disorders

Preferred Term	Number of Events[a,b,c,d]		
Age (years)	**< 18[e]**	**≥ 18[f]**	**NR[g]**
Abasia	1	-	-
Drooling	-	-	-(1)
Dystonia	-(1)	-	-
Extrapyramidal disorder	1	-	1
Muscle spasms	1(3)	2(2)	-(2)
Muscle tightness	-	-(1)	-
Muscle twitching	1(2)	-(1)	-(2)
Tic	7(6)	-(2)	4(5)
Tongue spasm	-(2)	-	-
Torticollis	-(1)	-	-
Trismus	-(1)	-(1)	-
Subtotal	**11(16)**	**2(7)**	**5(10)**
Total[h]	**51**		

Key: MPH=Methylphenidate hydrochloride, NR=Not reported, PT=Preferred term
a: Cases may have reported more than 1 event of interest
b: Events reported from medically confirmed cases
c: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified
d: Dash (-) indicates the specified PT was not identified within the age/age group
e: Includes patients < 18-years-old and/or patient age category: neonate, infant, adolescent, child
f: Includes patients ≥ 18-years-old and/or patient age category: adult, elderly
g: Includes patients with no reported age and age category
h: Includes serious and nonserious events

Thirty-nine cases (see Appendix 7.3 for case numbers) reported listed events of interest, including Tic (23 cases), Muscle spasms (9 cases), Muscle twitching (5 cases), and 1 case each of Tongue spasm and Muscle tightness.

An overview of the characteristics of 5 of the 9 remaining cases[135] that reported unlisted events (5 patients < 18-years-old) is presented in Table 42. One male patient was ≥ 18-years-old (adult) and reported taking an unspecified dose for an unspecified indication. Outcome of the event was not reported. The remaining 3 patients with no reported age/age category reported 1 female patient and 2 patients of unknown sex who received an unspecified dose for ADHD (2) or mental disorder indication. Outcome of the events were not reported.

[134] 20111207857, 20120710993, 20120804631, 20120814944, 20121000999

[135] 20121103158, 20121112054, 20121213686, 20130308991, 20130313199, 20130318317, 20130702172, 20131007591, 20131015194

Table 42: Characteristics for OROS MPH Cases Reporting Tics and Tourette's Disorder/Dystonia in Patients <18-years-old

Characteristic		Number of Cases (n=5)
Source	Spontaneous	5
Patient Sex	Male	4
	Female	1
Patient Age (Years)[a]	<5	0
	5 to 8	0
Mean: 11.6	9 to 13	4
Median: 12	14 to 17	1
Daily Dose at Onset of Adverse Event	27 mg	2
	36 mg	2
	54 mg	1
Indication	ADHD	4
	Not reported	1
Latency	< 1 week	0
	1 week to 1 month	0
	>1 month to 6 months	0
	> 6 months to 1 year	0
	>1 year	2
	Not reported	3
Outcome of Event of Interest[b]	Resolved	4
	Not resolved	1
	Not reported	1

Key: ADHD= Attention Deficit Hyperactivity Disorder; MPH= Methylphenidate hydrochloride; n= Number of cases
a: Patient age category provided for cases with no age reported.
b: Cases may contain > 1 event of interest.

All cases were medically reviewed. One case (no reported age/age category) was selected for presentation because of potential medical interest and is presented below.

Patients with no reported age/age category

- [redacted] **(*Muscle twitching*, *Tic*, Drug ineffective):** [redacted] of unspecified age received OROS methylphenidate HCl for ADHD; dose and frequency was not provided. Medical history and concomitant therapy were not reported. An unspecified time after initiating treatment, the patient experienced small twitches and tics in her fingers and feet. She also experienced lack of efficacy reported as, "crowd of thoughts starts again", when the "medication abate totally 12-13". Action taken with OROS methylphenidate HCl was not reported and event outcomes were not provided (see Section 16.2.2, Efficacy Related Information).

Discussion

A total of 48 cases suggestive of tics and Tourette's disorder/dystonia were reported during the current PSUR period. There were no cases reporting the PT Tourette's disorder. The majority of the cases, 81% (39/48), reported events that are listed in the CCDS. One case (20130308991) was identified for further review and involved a patient with unspecified age/age category. The limited information provided in this case precludes a thorough evaluation.

Conclusion

Review of the cases in this reporting period did not identify any patterns or new safety information with respect to tics, Tourette's disorder and dystonia. No changes to the CCDS or RMP are warranted at this time.

16.3.8. Reproductive and Breast Disorders

Introduction

Cases with events relevant to the reproductive system and breast disorders were selected for review due to potential medical significance. Erectile dysfunction and Libido decreased are listed ADRs in the CCDS.

On 09 October 2013, the Company received a Prior Approval Supplement (PAS) request from the US FDA for the addition of priapism and libido changes to the OROS methylphenidate HCl US package insert (USPI). The Company performed a cumulative ad-hoc analysis of all post-marketing and clinical trial cases of priapism and increased libido in the GMS database, to determine if there is a drug-event association between OROS methylphenidate HCl use and the occurrence of priapism or increased libido and the results of this review will be described in the next PBRER/PSUR. Based on this review, the cumulative weight of evidence was sufficient in supporting both priapism and increased libido as ADRs associated with the use of OROS methylphenidate HCl. In addition to biologic plausibility, the available safety data and literature review were key factors supporting the conclusion. Evaluation of these risks is ongoing.

The High Level Terms Erection & Ejaculation Conditions and Disorders and Sexual function & Fertility Disorders Not Otherwise Classified were selected to identify cases for review.

Erectile dysfunction is a listed event in the CCDS.

Results

The search described above identified 14[136] medically confirmed cases (13 initial, 1 follow-up). Of the medically confirmed cases, a review of the follow-up case did not change the prior assessment of the event in this case; therefore, this case is not discussed further.

[redacted]

Table 43 displays a count of the selected PTs by age and seriousness in the remaining 13 cases included in the current PSUR reporting period.

Table 43: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Reproductive System and Breast Disorders

Preferred Term	Number of Events[a,b,c,d]		
Age (years)	**< 18[e]**	**≥ 18[f]**	**NR[g]**
Erectile dysfunction	-(1)	-(5)	-(1)
Hypogonadism	-	1	-
Libido decreased	-	-(2)	-
Libido increased	-(1)	1	-
Precocious puberty	1	-	-
Priapism	1	-	-
Spontaneous ejaculation	-	1	-
Subtotal	**2(2)**	**3(7)**	**-(1)**
Total[h]	**4**	**10**	**1**

Key: MPH=Methylphenidate hydrochloride, NR=Not reported, PT=Preferred term
a: Cases may have reported more than 1 event of interest
b: Events reported from medically confirmed cases
c: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified
d: Dash (-) indicates the specified PT was not identified within the age/age group
e: Includes patients < 18-years-old and/or patient age category: neonate, infant, adolescent, child
f: Includes patients ≥ 18-years-old and/or patient age category: adult, elderly
g: Includes patients with no reported age and age category
h: Includes serious and nonserious events

Seven cases[137] reported listed events of interest, including Erectile dysfunction (7) and Libido decreased (2). Of [redacted]) reported 2 events of interest.

An overview of the characteristics of the remaining 6 cases[138] (3 patients < 18-years-old and 3 patients ≥ 18-years-old) is presented in Table 44 and Table 45, respectively.

[redacted]

[redacted]

Table 44: Characteristics for OROS MPH Cases Reporting Reproductive System and Breast Disorders in Patients <18-years-old

Characteristic		Number of Cases (n=3)
Source	Spontaneous Literature	2 1
Patient Sex	Male	3
Patient Age (Years) **Mean:** 11.3 **Median:** 12	9 to 13	3
Daily Dose at Onset of Adverse Event	18 mg 27 mg	2 1
Indication	ADHD	3
Latency	Not reported	3
Outcome of Event of Interest[a]	Not resolved Not reported	1 2

Key: ADHD= Attention Deficit Hyperactivity Disorder; MPH= Methylphenidate hydrochloride; n= Number of cases
a: Cases may contain > 1 event of interest.

Table 45: Characteristics for OROS MPH Cases Reporting Reproductive System and Breast Disorders in Patients ≥18-years-old

Characteristic		Number of Cases (n=3)
Source	Spontaneous Literature	2 1
Patient Sex	Male Female	2 1
Patient Age (Years)[a] **Mean:** 42.5	18 to 35 36 to 54 55 to 64 ≥65 "Adult"	1 0 1 0 1
Daily Dose at Onset of Adverse Event	18 mg Not reported	2 1
Indication	ADHD Disturbance in attention Fatigue Not reported	1 1 1 1
Latency	<2 weeks Not reported	1 2
Outcome of Event of Interest[b]	Resolved Resolving Not reported	1 1 1

Key: ADHD= Attention Deficit Hyperactivity Disorder; MPH= Methylphenidate hydrochloride; n= Number of cases
a: Patient age category provided for cases with no age reported.
b: Cases may contain > 1 event of interest.

All cases were medically reviewed, and 6 cases (3 patients <18-years-old and 3 patients ≥18-years-old) were selected for presentation because of potential medical interest. These cases are presented in Table 46 below.

Table 46: Selected OROS MPH Cases Reporting Reproductive and Breast Disorders

AER# Country Age (years)/Sex	Indication Daily Dose[a] Latency[b]	Adverse Events (MedDRA PTs)[c]	*Co-suspect*[d]/ Concomitant Medications	Medical History	Comments
Patients < 18-years-old					
[redacted] Turkey [redacted]	ADHD 18 mg NR	**Precocious puberty** Hypersensitivity	*MPH*/ NR	NR	The patient was treated with OROS MPH, but temporarily discontinued the medications for 1 month in 2011, and was treated with MPH. That same year when the patient was 9 years old, he experienced precocious puberty characterized by facial acne, hair growth on scrotum, nervousness, and spotting on the nose. Treatment included triptorelin. Action taken with OROS MPH or MPH was not reported. Event was not resolved (see also Section 16.3.5.2.4, Use in Children).
[redacted] Ireland [redacted]	ADHD 36 mg NR	**Priapism**	*NR*/ NR	NR	An unspecified time after initiating OROS MPH, the patient experienced prolonged painful erections unaccompanied by sexual excitation for 2 years. He experienced approximately 3 short-lived erections per day. There was no bladder, bowel or neurological symptoms. No abnormalities were detected on examination of abdomen, spine or lower limbs. Testicular volume for age was normal. No abnormalities were found on investigation of other causes of priapism. Testosterone levels were normal. OROS MPH was discontinued. Event outcome was not reported (see also Section 16.3.5.2.4, Use in Children).
[redacted] Switzerland [redacted]	ADHD 27 mg NR	Weight decreased **Libido increased**	*NR*/ NR	NR	The patient experienced increased libido with sexual fantasies an unspecified time after initiating OROS MPH. It was reported that the patient became sexually active (activities unspecified). Action taken with OROS MPH was not reported. Event outcome was not specified (see also Section 16.3.5.2.4, Use in Children).
Patients > 18-years-old					
[redacted][f] Netherlands [redacted]	NR NR NR	**Spontaneous ejaculation** Testicular pain	*MPH*/ NR	Spontaneous ejaculation (while using atomoxetine)	An unspecified time after initiating OROS MPH, the patient experienced spontaneous ejaculation without sexual arousal following testicular pain after micturition. OROS MPH and MPH were discontinued. The spontaneous ejaculations were ongoing, but were less frequent.

Table 46: Selected OROS MPH Cases Reporting Reproductive and Breast Disorders

AER# Country Age (years)/Sex	Indication Daily Dose[a] Latency[b]	Adverse Events (MedDRA PTs)[c]	*Co-suspect*[d]/ Concomitant Medications	Medical History	Comments
[redacted] United States [redacted]	Fatigue Disturbance in attention 18 mg NR	Pituitary tumour Peyronie's disease **Hypogonadism**	*Sertraline* *Clonazepam* *Bupropion*/ NR	Alcohol use Anxiety Arthritis Depression Hypersensitivity Osteoarthritis	An unspecified time after initiating OROS MPH, the patient experienced pituitary tumour, Peyronie's disease, hypogonadism and low testosterone levels (below 200 [units not specified]) with subsequent loss of appetite. OROS MPH was discontinued due to loss of appetite. Outcome for hypogonadism was not reported (see Section 16.2.1.2, Neoplasms, Benign, Malignant and Unspecified [Including Cysts and Polyps], and Section 16.3.5.2.3, Use in the Elderly).
[redacted] Sweden [redacted]	ADHD 18 mg 2 weeks	Delusion Hallucination, tactile **Libido increased** Anger Delusion Affect lability Hallucination, auditory	*NR*/ Amitriptyline	Appendicectomy Intestinal operation Pain Sleep disorder Injury	Approximately 2 weeks after initiating OROS MPH, the patient experienced constellation of events including increased libido. The patient believed the events were associated with childhood trauma (unspecified). OROS MPH was discontinued for 2 days, and later restarted. The event was resolving.

Key: AER#= Adverse event report number; ADHD= Attention Deficit Hyperactivity Disorder; MedDRA= Medical Dictionary for Regulatory Activities; MPH= Methylphenidate hydrochloride; NR= Not reported, PT= Preferred term

a: Daily dose at the time of the event of interest.

b: Time from the first exposure to OROS MPH to onset of event of interest.

c: Events of interest are in **bold**.

d: Co-suspect medications are *italicised.*

e: Kelly BD, Lundon DJ, Brady CM. Methylphenidate-induced erections in a prepubertal child. J Pediatr Uurol 2013; 9 (1): e 1-2

f: Oosterhuis I, Heijting L, Puijenbroek Ev. Spontaneous ejaculation with the use of noradrenergic reuptake inhibitors. *Eur J Clin Pharmacol* 2012; 68(10):1461-1462

Discussion

Erectile dysfunction and libido decreased are currently listed in the CCDS as an ADR for OROS methylphenidate HCl based on clinical trial data in adult patients.

Patients <18-years-old

The 3 cases that were evaluated involved precocious puberty, priapism and libido increased in male patients ranging in age between 9 and 12 years. All 3 cases lacked information regarding latency, medical history, concomitant therapy, action taken with OROS methylphenidate HCl, and/or event outcome. [redacted]eported precocious puberty characterized by facial acne, hair growth on scrotum, nervousness, and "spotting on the nose". Precocious puberty is defined as precocious development of sexual hair (pubic hair, axillary hair or both) before 8 years of age in girls or 9 years of age in boys, with no other signs of sexual maturation.[139] The condition is due to premature secretion of adrenal androgen and the patient's treatment included triptorelin. The remaining 2 cases reported 1 event each of increased libido and priapism. The association with OROS methylphenidate HCl is difficult to assess with the information provided, however, both events have been reported with methylphenidate-containing products.

Patients ≥18-years-old

The 3 cases that were evaluated involved spontaneous ejaculation, hypogonadism and increased libido. Assessment of the case was confounded in [redacted]) by medical history of spontaneous ejaculation while receiving atomoxetine or increased libido reported as secondary to unspecified childhood trauma, respectively. The event of Hypogonadism experienced by the patient in [redacted] was likely secondary to the diagnosed pituitary tumour. An adequate medical assessment of the cases could not be made due to general lack of detailed, descriptive information regarding the events.

Conclusion

Review of the cases in this reporting period did not identify additional patterns or new safety information with respect to reproductive system and breast disorders. The results of a cumulative ad-hoc analysis of all post-marketing and clinical trial cases of priapism and increased libido will be reported in the next OROS methylphenidate HCl PBRER/PSUR.

16.3.9. Skin and Subcutaneous Disorders

Introduction

Events in this SOC were reviewed due to potential medical significance. The following Skin and Subcutaneous Tissue Disorders are noted in the CCDS, Adverse Events Section: Alopecia, Erythema, Hyperhidrosis, Rash, and Rash Macular. In addition, the following hypersensitivity reactions are noted in the Adverse Events Section: angioedema, bullous conditions, exfoliative conditions, rashes, pruritus, exanthemas, and eruptions.

[139] Traggiai C, Stanhope R. Disorders of pubertal development. *Best Prac Res Cl Ob.* 2003;17(1): 41-56.

The following MedDRA PTs were selected to identify cases for review: Stevens-Johnson Syndrome (SJS) and Hyperhidrosis. Hyperhidrosis is a listed event in the CCDS.

Results

The search described above identified 10 initial cases[140] (no follow-up). Table 47 displays a count of the selected PTs by age and seriousness in the 10 cases received for the current PSUR reporting period.

Table 47: Interim Count of Selected PTs by Age and Seriousness in Cases With OROS MPH: Skin and Subcutaneous Tissue Disorders

Preferred Term	Number of Events[a,b]		
Age (years)	**<18[c]**	**≥18[d]**	**NR[e]**
Hyperhidrosis	-(1)	-(5)	-(3)
Stevens-Johnson syndrome	-	-	1
Subtotal	**(1)**	**(5)**	**1 (3)**
Total[f]	**10**		

Key: MPH= Methylphenidate hydrochloride; NR= Not reported, PT= Preferred term

a: Nonserious cases are presented in parentheses. If no parentheses are observed, then zero nonserious cases were identified
b: Dash (-) indicates the specified PT was not identified within the age/age group
c: Includes patients <18-years-old and/or patient age category: neonate, infant, adolescent, child.
d: Includes patients ≥18-years-old and/or patient age category: adult, elderly.
e: Includes patients with no reported age and age category.
f: Includes serious and nonserious cases.

Nine[141] of the 10 cases reported the nonserious listed event of Hyperhidrosis, of which 1 case involved a patient aged under 18 years, 5 involved adult patients aged over 18 years, and 3 involved patients of unspecified age. The remaining case reported the serious unlisted event of SJS in a patient of unspecified age and is presented below.

Patients with no reported age/age category

- [redacted] **(Stevens-Johnson syndrome)**: [redacted] was treated with OROS methylphenidate HCl for an unspecified indication. Dose, medical history, and concomitant medications were not reported. On an unspecified date, the patient experienced SJS. The action taken with OROS methylphenidate HCl and the outcome of the event was not reported.

[redacted]

[redacted]

Discussion

Patients with no reported age/age category

[redacted] reported an event of SJS, but provided no details on patient medical history, concomitant medication, latency, clinical course of the event, action taken, or outcome, thereby precluding medical assessment.

Conclusion

The data presented in this interval review of PTs in the Skin and Subcutaneous Tissue Disorders SOC provides insufficient evidence to confirm that the reported skin disorders represent a new safety concern. No changes to the CCDS are recommended at this time.

16.4. Characterisation of Risks

There is an EU-RMP for OROS methylphenidate HCl and the current version is dated 10 Dec 2012. The table of risks refers to the final core table of identified and potential risks referred to in the Rapporteur's 03 December 2008 Assessment Report (of the Article 31 safety referral for methylphenidate) and is common to the RMPs of all methylphenidate-containing medicinal products in the EU. The list was referenced and adopted in the European Commission decision for the safety referral on 27 May 2009.

Listed below are the important identified risks in the EU RMP for methylphenidate containing products relevant to the approved indication of ADHD.

- Hypertension
- Tachycardia
- Raynaud's phenomenon
- Hallucinations (auditory, skin sensation, visual disturbance)
- Psychosis/Mania
- Anorexia
- Decreased rate of growth
- Aggression
- Depression

These identified risks are characterised in Table 48 to Table 55. Of these risks, psychosis (of the combined Psychosis/Mania identified risk), Decreased rate of growth and Tactile hallucinations were not identified as ADRs for OROS methylphenidate HCl based on clinical trials or postmarketing surveillance. Decreased rate of growth is not presented below.

Table 48: Important Identified Risk: Hypertension

Identified Risk: Hypertension*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	1 (0.3)	19 (0.7)
vs	VS	
Placebo (N=318)	0 (0.0)	
Odds Ratio	NA	NA
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	1
Discontinued Treatment	0	4
Resolved/Recovered/Recovered From AE	1	8
Recovered With Residual Effects	0	1
Continuing/Not Yet Recovered	0	3
Severity****		
Mild	0	17
Moderate	1	1
Severe	0	1

* MedDRA (Medical Dictionary for Regulatory Activities) preferred terms searched for this risk are provided in Annex 5 of the RMP.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hypertension. The subject is counted only once regardless of the number of events or the number of occurrences.

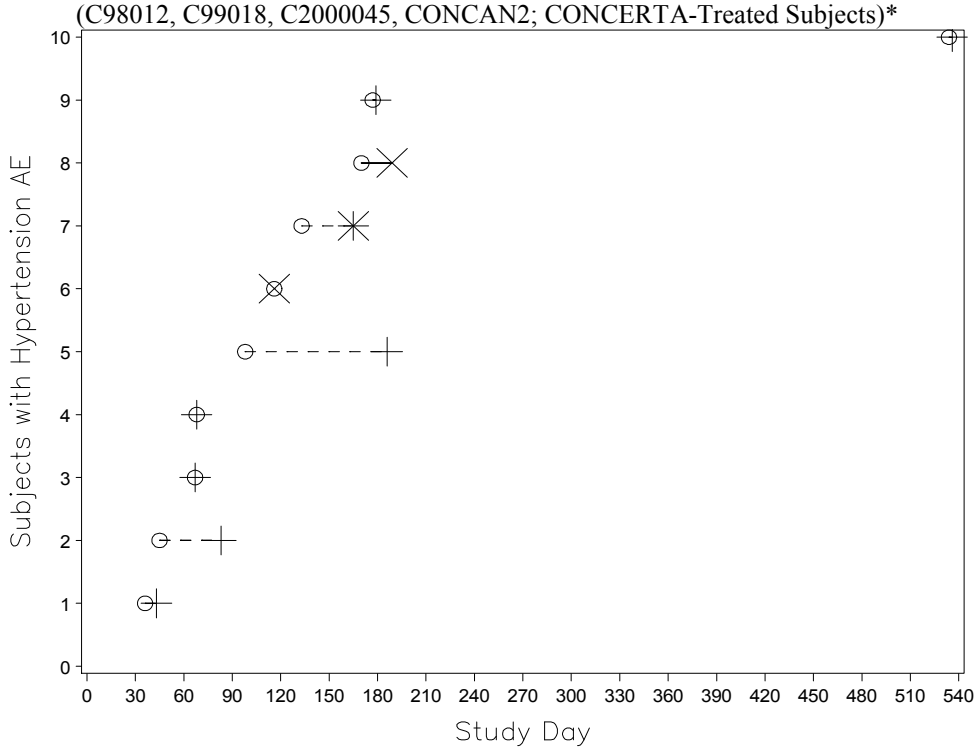
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was established for Hypertension and Blood pressure increased. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Table 48: Important Identified Risk: Hypertension (Continued)

Onset and Duration of Hypertension: Open-Label Trials of at Least 3 Months Duration (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)

Day	270	300	330	360	390	420	450	480	510	540
N	809 (51)	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

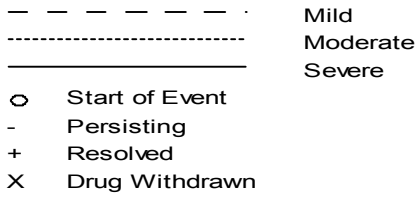


Table 48: Important Identified Risk: Hypertension (Continued)

Postmarketing:

Cumulative Count of Events for the Important Identified Risk of Hypertension Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of Events	
Important Identified Risk:	**Nonserious[a]**	**Serious[a]**
Hypertension	164	161

[a] At event level

Source: Global Medical Safety database (SCEPTRE).

Background incidence/prevalence	No published reports showing an increased prevalence of hypertension in children or adolescents, diagnosed with ADHD have been identified. In the general population, as a mechanism to provide background rates, screening surveys of junior and high school-aged children have found the prevalence of hypertension to be between 1% and 2%. A review of studies performed in referral centres suggests that the frequency of primary hypertension among children is increasing over time.[a,b,c,d] The proportion of all hypertension in children that was classified as primary has increased from 16% in 1988 to 23% in 1994, and most recently was reported as 48.6%.
Risk groups or risk factors	No published reports indicating an increased risk for hypertension in children with ADHD have been identified. Two population-based studies have looked at the relationship of overweight (defined as ≥95th percentile of body mass index (BMI) in Curtin et al study and ≥90th percentile in the Holtkamp et al study) obesity (ie, as cardiovascular risk factor, defined in the Holtkamp et al study as ≥97th percentile of BMI) and ADHD in children.[e,f] One study found ADHD children were more likely to be obese, while the second did not.
Potential mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases.
Preventability	Early detection, monitoring and therapy including pharmacotherapy, nutritional and life style changes. Patient's blood pressure should be monitored at appropriate intervals if CONCERTA® is prescribed, especially if the patient has hypertension. Blood pressure and pulse should be recorded at each adjustment of dose and subsequently as clinically needed. Use appropriate caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.
Potential public health impact of safety concern	The clinical trial database and the postmarketing database demonstrate CONCERTA® treatment confers a risk of small increases in blood pressure and heart rate. Given that CONCERTA® is a sympathomimetic compound, these are pharmacologically-expected effects. Clinically significant increases in blood pressure are not expected. If a clinically significant blood pressure increase occurs and is believed to be drug related, CONCERTA® therapy should be discontinued and the effect will dissipate. The overall number of individuals affected is small. Therefore, drug-induced increases in blood pressure are not expected to have an impact with respect to overall public health.

Table 48: Important Identified Risk: Hypertension (Continued)

Regulatory Action Taken	European Union: Annex IV of the May 2009 EC Decision states that the report of the FDA/AHRQ/Vanderbilt University pharmacoepidemiologic study should be evaluated. This action is complete. Amendments were made to the SmPC following an Article 31 referral procedure for methylphenidate in the EU which concluded on 27 May 2009: This includes pre-treatment screening and ongoing monitoring recommendations at Section 4.2 and Section 4.4 of the SmPC.

Key: ADHD=Attention Deficit Hyperactivity Disorder, AHRQ=Agency for Healthcare Research and Quality, EC=European Commission, EU=European Union, FDA=Food and Drug Administration, SmPC=Summary of Product Characteristics

a: Flynn JT. Characteristics of children with 1º HTN referred to a tertiary center. *Am J Hypertens* 2001;14:239A
b: Feld LG, Springate JE. Hypertension in children. *Curr Probl Pediatr* 1988;18:317-373
c: Arar MY (1994), Hogg RJ, Arant BS Jr, Seikaly MG. Etiology of sustained hypertension in children in the southwestern United States. *Pediatr Nephrol* 1994;8:186-189
d: Flynn JT. What's new in pediatric hypertension? *Curr Hypertens Rep* 2001;3:503-510 B7
e: Holtkamp K (2004), Konrad K, Muller B, et al. Overweight and obesity in children with Attention Deficit/Hyperactivity Disorder. *Int J Obes Relat Metab Disord* 2004;28(5):685-689
f: Curtin C (2005), Bandini LG, Perrin EC, Tybor DJ, Must A. Prevalence of overweight in children and adolescents with attention deficit hyperactivity disorder and autism spectrum disorders: a chart review. *BMC Pediatr* 2005;5:48

Table 49: Important Identified Risk: Tachycardia

Identified Risk: Tachycardia*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	0	7 (0.3)
vs		
Placebo (N=318)	0	
Odds Ratio	NA	NA
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	1
Resolved/Recovered/Recovered From AE	0	5
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	2
Severity****		
Mild	0	2
Moderate	0	4
Severe	0	1

* MedDRA preferred terms searched for this risk are provided in Annex 5.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Tachycardia. The subject is counted only once regardless of the number of events or the number of occurrences.

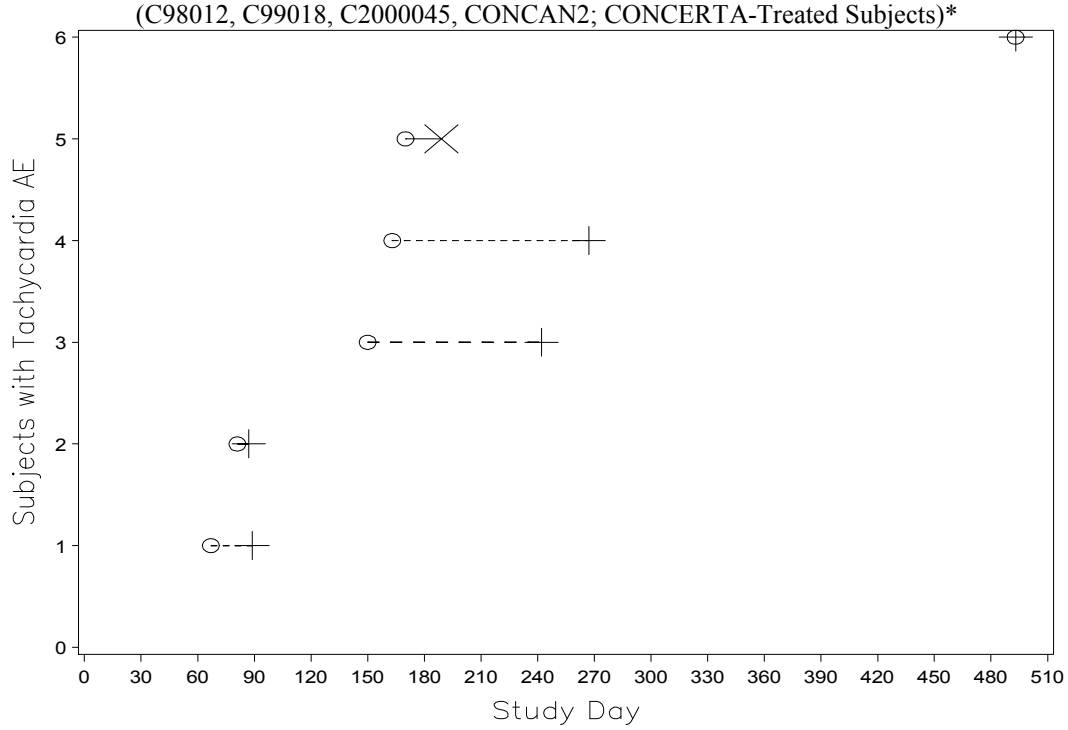
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCL, a causal relationship was established for Tachycardia. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Table 49: Important Identified Risk: Tachycardia (Continued)

Onset and Duration of Tachycardia: Open-Label Trials of at Least 3 Months Duration
(C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)

Day	270	300	330	360	390	420	450	480	510
N	809 (51)	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

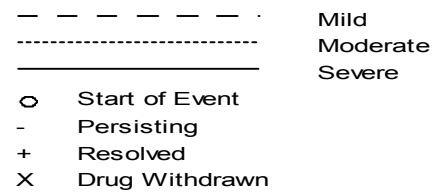


Table 49: Important Identified Risk: Tachycardia (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Tachycardia Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of Events	
Important Identified Risk:	**Nonserious[a]**	**Serious[a]**
Tachycardia	100	146

[a] At event level

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for this risk are provided in Annex 5.

Background Incidence/ Prevalence	No published reports of an association between arrhythmias and ADHD have been identified. In the general population, a study that included 26 US community emergency departments (ED) and 2.3 million ED visits found that primary cardiac arrhythmias in those under 18 years of age was an infrequent presentation to the ED.[a] The incidence of clinically significant arrhythmias in these patients was reported as 5.7 per 100,000 ED visits. Atrial tachyarrhythmias were the most common presentation in this study population.
Risk Group or Risk Factors	No published reports indicating an increased risk in children with ADHD for arrhythmias, including tachycardia have been identified.
Potential Mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases.
Preventability	Education of patients, caregivers and prescribers. Early detection, monitoring and therapy, including life style changes (avoid stimulants such as caffeine, nicotine, some decongestants and illegal drugs). Use appropriate caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.

(Continued)

Table 49: Important Identified Risk: Tachycardia (Continued)

Potential Public Health Impact of Safety Concern	The clinical trial database and the postmarketing database demonstrate CONCERTA® treatment confers a risk of small increases in heart rate. Given that CONCERTA® is a sympathomimetic compound, these are pharmacologically-expected effects. The overall number of individuals affected is small and the pharmacologic effect dissipates when the drug is withdrawn. Therefore, increased heart rate is not expected to have an impact with respect to overall public health.
Regulatory Action Taken	European Union: Annex IV of the May 2009 EC Decision states that the report of the FDA/AHRQ/Vanderbilt University pharmacoepidemiologic study should be evaluated (Table 21). This action is complete. Amendments were made to the SmPC following an Article 31 referral procedure for methylphenidate in the EU which concluded on 27 May 2009: This includes pre-treatment screening and ongoing monitoring recommendations at Section 4.2 and Section 4.4 of the SmPC.

Key: ADHD=Attention Deficit Hyperactivity Disorder, EC=European Commission, ED=Emergency department, EU=European Union, SmPC=Summary of Product Characteristics

a: Sacchetti A (1999), Moyer V, Baricella R, Cameron J, Moakes ME. Primary cardiacarrhythmias in children. *Pediatr Emerg Care* 1999;15 (2):95-98.

Table 50: Important Identified Risk: Raynaud's phenomenon

Identified Risk: Raynaud's Phenomenon*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	0	1 (0.0)
vs		
Placebo (N=318)	0	
Odds Ratio	NA	NA
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	0
Resolved/Recovered/Recovered From AE	0	1
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	0
Severity****		
Mild	0	0
Moderate	0	1
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Raynaud's phenomenon. The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCL, a causal relationship was not established for the adverse event that may be relevant for this important identified risk.

(Continued)

Table 50: Important Identified Risk: Raynaud's phenomenon (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Raynaud's Phenomenon Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

Important Identified Risk	Number of Events	
	Nonserious[a]	Serious[a]
Raynaud's Phenomenon	97	73

[a] At event level.

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for this risk are provided in Annex 5 of the RMP.

Background incidence/prevalence	No published reports indicating an increased prevalence of Raynaud's phenomenon in children or adolescents diagnosed with ADHD have been identified. In the general population, a population-based study of 720 children, ages 12 to 15 years, in England found that 14.9% reported symptoms consistent with Raynaud's disease. The prevalence was higher in adolescent girls (17.6%) than in adolescent boys (12.2%), and increased with age. The Framingham Offspring Study cohort consisted of 1,358 adults (mean age=53.5) that were followed for a mean of 7.1 years.[a] At baseline, 10.9% of girls and 7.8% of boys were found to have Raynaud's disease. During follow up, new, incident Raynaud's disease was observed in 2.2% of adolescent girls and 1.5% of adolescent boys.[b]
Risk groups or risk factors	No published reports indicating an increased risk of Raynaud's disease in children or adolescents with ADHD have been identified.
Potential mechanisms	Methylphenidate is a catecholaminergic agent (noradrenergic and dopaminergic) and has sympathomimetic properties. Sympathomimetics can induce heart rate and blood pressure increases.
Preventability	Protection from cold.
Potential public health impact of safety concern	There was a single report of Raynaud's phenomenon in the clinical trials database. A recent report of "possible Raynaud's" in both the hands and feet of a teenage boy occurred after the dosage of CONCERTA® was increased from 54 to 90 mg/day over a 3-month period.[c] Although very rarely reported in the spontaneous postmarketing database, the pharmacologic mechanism and the evidence analysis of cases are consistent with a possible causal association between CONCERTA® and Raynaud's phenomenon. However, this effect is reversible in nature and is not expected to have an impact with respect to overall public health.
Regulatory action taken	European Union: None

Key: ADHD=Attention Deficit Hyperactivity Disorder

a: Jones GT, Herrick AL, Woodham SE, Baildam EM, Macfarlane GJ, Silman AJ. Occurrence of Raynaud's phenomenon in children ages 12-15 years: prevalence and association with other common symptoms. *Arthritis Rheum* 2003;48(12): 3518-3521

b: Suter LG (2005), Murabito JM, Felson DT, Fraenkel L. The incidence and natural history of Raynaud's phenomenon in the community. *Arthritis Rheum* 2005;52(4):1259-1263

c: Yu ZJ (2010), Parker-Kotler C, Tran K, Weller RA, Weller EB. Peripheral vasculopathy associated with psychostimulant treatment in children with attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep* 2010;12:111–115

Table 51: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance)

Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance)*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	0	3 (0.1)
vs		
Placebo (N=318)	0	
Odds Ratio	NA	NA
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	1
Discontinued Treatment	0	1
Resolved/Recovered/Recovered From AE	0	2
Recovered With Residual Effects	0	0
Continuing/Not Yet Recovered	0	1
Severity****		
Mild	0	1
Moderate	0	2
Severe	0	0

* MedDRA preferred terms searched for this risk are provided in Annex 5.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Hallucinations (Auditory, skin sensation, visual disturbance). The subject is counted only once regardless of the number of events or the number of occurrences.

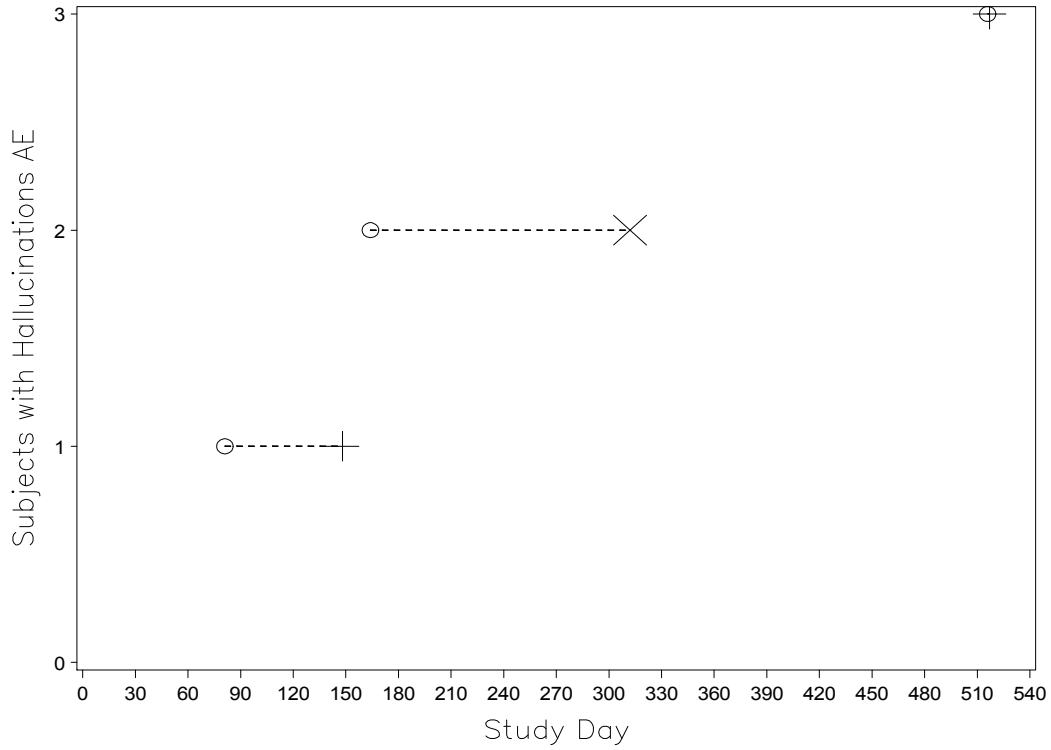
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

Table 51: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance) (Continued)

Onset and Duration of Hallucinations: Open-Label Trials of at Least 3 Months Duration (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)

Day	270	300	330	360	390	420	450	480	510	540
N	809 (51)	396 (25)	345 (22)	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

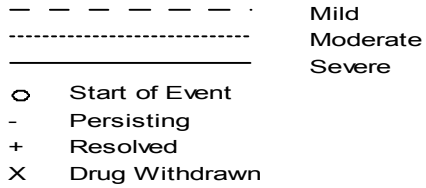


Table 51: Important Identified Risk: Hallucinations (Auditory, Skin Sensation, Visual Disturbance) (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Hallucination (Auditory, Skin Sensation, Visual Disturbance) Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of events	
Important Identified Risk	**Nonserious[a]**	**Serious[a]**
Hallucination (Auditory, Skin Sensation, Visual Disturbance)	116	309

[a] At event level.

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for this risk are provided in Annex 5.

Background incidence/prevalence	No published reports on the frequency of psychosis, including hallucinations, in young persons with ADHD have been identified.
Risk groups or risk factors	In the published literature, children and adolescents with ADHD were found to have a high prevalence of comorbid psychiatric disorders (oppositional defiant disorder, major depression, anxiety, mania, psychosis).
Potential mechanisms	CONCERTA® is known to increase dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters have important roles in the aetiology of psychiatric symptoms. While the specific pathways that are responsible for stimulant-induced psychosis, for example, are not mapped out in detail, the pharmacological basis of this ADR is well accepted.
Preventability	Education of prescribers. Early detection and management of psychiatric symptoms. Methylphenidate should not be prescribed to patients with psychotic disorder. Caution should be exercised in patients with comorbid psychiatric disorders. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent.
Potential public health impact of safety concern	In the CONCERTA® clinical trial database, visual, auditory, and tactile hallucinations have been reported rarely in patients with ADHD without a previous history of psychosis; the event is transient, resolves fully upon discontinuation of the medication, and is sometimes related to concomitant abuse of an intoxicating substance. The overall number is small and due to its reversible nature it is not expected to have an impact with respect to overall public health.
Regulatory action taken	European Union: Amendments were made to the SmPC following an Article 31 referral procedure for methylphenidate in the EU which concluded on 27 May 2009: This includes pre-treatment screening and ongoing monitoring recommendations at Section 4.2 and Section 4.4 of the SmPC.

Key: ADHD=Attention Deficit Hyperactivity Disorder, ADR=Adverse drug reaction, EU=European Union, SmPC=Summary of Product Characteristics

Table 52: Important Identified Risk: Psychosis/Mania

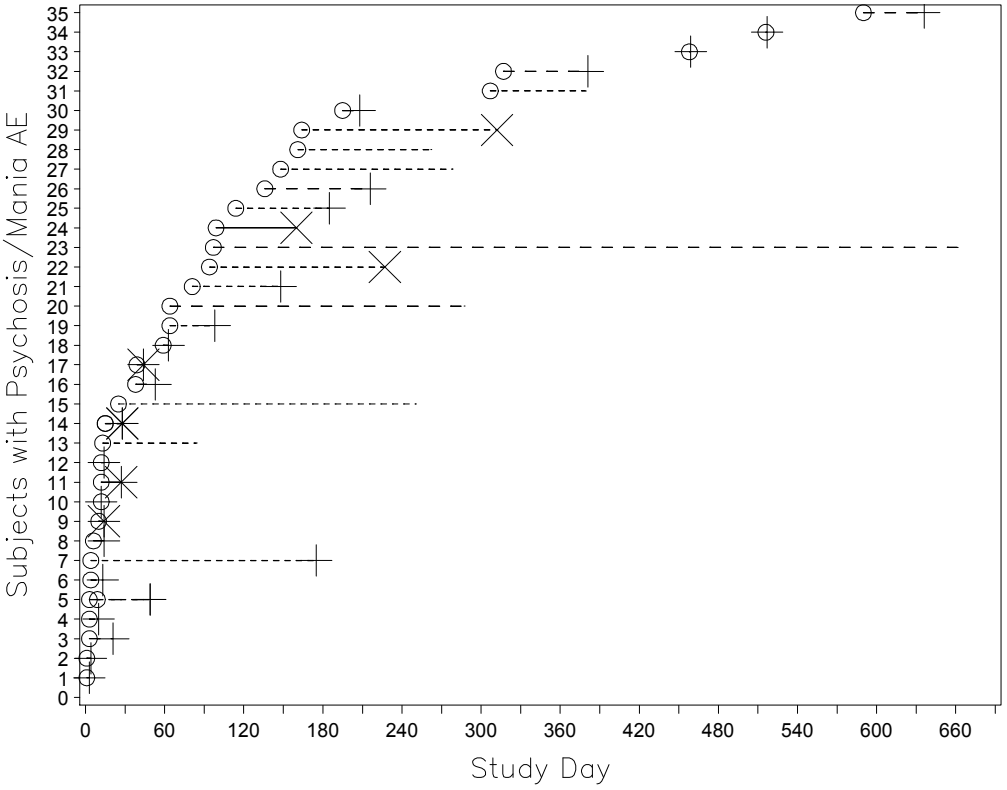
Identified Risk: Psychosis/Mania*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	1 (0.3)	76 (2.8)
vs	VS	
Placebo (N=318)	0 (0.0)	
Odds Ratio	NA	NA
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	5
Discontinued Treatment	0	15
Resolved/Recovered/Recovered From AE	1	45
Recovered With Residual Effects	0	1
Continuing/Not Yet Recovered	0	25
Severity****		
Mild	0	32
Moderate	1	34
Severe	0	9

* MedDRA preferred terms searched for this risk are provided in Annex 5.
** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Psychosis/Mania. The subject is counted only once regardless of the number of events or the number of occurrences.
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.
**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was not established for any of the adverse events that may be relevant for this important identified risk.

Table 52: Important Identified Risk: Psychosis/Mania (Continued)

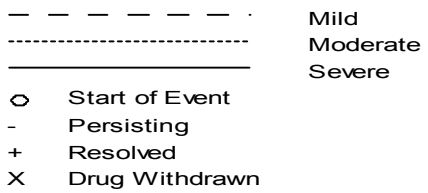
Onset and Duration of Psychosis/Mania: Open-Label Trials of at Least 3 Months Duration
(C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)*



Day	0	30	60	90	120	150	180	210	240	270	300	330
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)

Day	360	390	420	450	480	510	540	570	600	630	660	690
N	296 (19)	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.



(Continued)

Table 52: Important Identified Risk: Psychosis/Mania (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Psychosis/Mania Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of Events	
Important Identified Risk	**Nonserious[a]**	**Serious[a]**
Psychotic disorder/Mania	859	712

[a]At event level

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for these risks are provided in Annex 5.

Background incidence/prevalence	No published reports on the frequency of psychosis, including mania, in young persons with ADHD have been identified. A prospective 8-year follow up of adolescents (mean age 16.8 [SD 1.0] years) initially enrolled as children in the MTA study found too few reports of psychosis and mania (and hypomania) for reliable statistical analysis; prevalence (≥1 of these conditions) was 2.0% for those receiving medication management, 0.9% for those receiving behavioural therapy, and 2.9% for those receiving combined management.[a]
Risk groups or risk factors	In the published literature, children and adolescents with ADHD were found to have a high prevalence of comorbid psychiatric disorders (oppositional defiant disorder, major depression, anxiety, mania, psychosis).
Potential mechanisms	CONCERTA® is known to increase dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters have important roles in the aetiology of certain psychiatric symptoms including mood disorders, impulse-control disorders, psychosis, attention disorders, and anxiety disorders. While the specific pathways that are responsible for stimulant-induced psychosis, for example, are not mapped out in detail, the pharmacological basis of this ADR is well accepted.
Preventability	Education of prescribers. Early detection and management of psychiatric symptoms. Methylphenidate should not be prescribed to patients with psychotic disorder. Caution should be exercised in patients with comorbid psychiatric disorders. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent.
Potential public health impact of safety concern	In the CONCERTA® clinical trial database, psychotic and manic symptoms have been reported in patients with ADHD without a previous history of psychosis; the event is transient, resolves fully upon discontinuation of the medication, and is sometimes related to concomitant abuse of an intoxicating substance. The overall number is small and due to its reversible nature it is not expected to have an impact with respect to overall public health.
Regulatory action taken	European Union: Amendments were made to the SmPC following an Article 31 referral procedure for methylphenidate in the EU which concluded on 27 May 2009: This includes pre-treatment screening and ongoing monitoring recommendations at Section 4.2 and Section 4.4 of the SmPC.

Key: ADHD=Attention Deficit Hyperactivity Disorder, ADR=Adverse drug reaction

a: Molina BSG (2009), Hinshaw SP, Swanson JM, et al. MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500

Table 53: Important Identified Risk: Anorexia

Identified Risk: Anorexia*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	6 (1.9)	293 (10.8)
vs	VS	
Placebo (N=318)	0 (0.0)	
Odds Ratio	NA	NA
95% confidence interval***		
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	26
Resolved/Recovered/Recovered From AE	2	131
Recovered With Residual Effects	0	5
Continuing/Not Yet Recovered	4	121
Severity****		
Mild	5	176
Moderate	1	107
Severe	0	6

* MedDRA preferred terms searched for this risk are provided in Annex 5.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Anorexia. The subject is counted only once regardless of the number of events or the number of occurrences.

*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was established for Anorexia and Decreased appetite. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Table 53: Important Identified Risk: Anorexia (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Anorexia Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

Important Identified Risk	Number of Events	
	Nonserious[a]	Serious[a]
Anorexia	1,492	96

[a]At event level
Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for these risks are provided in Annex 5.

Background Incidence/ Prevalence	No published rates of anorexia among children with ADHD have been identified. For the general population, in 2000 the age- and gender-adjusted incidence of anorexia nervosa diagnosed in primary care was 4.7 per 100,000 population. The highest incidence, 34.6 per 100,000 population, was found in girls/adolescent girls aged 10 to 19 years.[a]
Risk Groups or Risk Factors	Data available from CONCERTA® clinical trials do not indicate any group is at particular risk for anorexic symptoms, whereas the disease, anorexia nervosa, primarily affects girls/women.
Potential Mechanisms	Central acting stimulants, such as methylphenidate have previously been found to produce weight loss in early studies of patients with narcolepsy, and have subsequently been used in the treatment of obesity. The drug promotes weight loss by suppressing appetite, rather than by increasing energy expenditure. Therefore, based on its pharmacologic effect, CONCERTA® may cause appetite suppression that is fully reversible when the medication is discontinued. This appetite suppression is distinct from the disease of anorexia nervosa.
Preventability	Education of prescribers, patients and caregivers. Early detection and management of symptoms (counselling, encouraging a healthy attitude to eating and weight). Also, the EU SmPC advises that appetite should be monitored during methylphenidate treatment and that patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted (Section 4.4).
Potential Public Health Impact of Safety Concern	Since appetite suppression is an acute and limited effect, it may in fact be of no consequence in most individuals. If appetite suppression becomes a concern due to low body weight, discontinuing the methylphenidate will fully reverse the effect; therefore, this is expected to have minimal public impact or safety concern.
Regulatory Action Taken	European Union: None

Key: ADHD=Attention Deficit Hyperactivity Disorder, EU=European Union, SmPC=Summary of Product Characteristics

a: Currin L (2005), Schmidt U, Treasure J, Jick H. Time trends in eating disorder incidence. *Br J Psychiatry* 2005;186:132-135

Table 54: Important Identified Risk: Aggression

Identified Risk: Aggression*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	3 (0.9)	192 (7.1)
vs	VS	
Placebo (N=318)	7 (2.2)	
Odds Ratio	0.4	NA
95% confidence interval***	0.1 to 1.9	
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	9
Discontinued Treatment	0	50
Resolved/Recovered/Recovered From AE	0	119
Recovered With Residual Effects	0	3
Continuing/Not Yet Recovered	1	51
Severity****		
Mild	1	60
Moderate	2	108
Severe	0	21

* MedDRA preferred terms searched for this risk are provided in Annex 5

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Aggression. The subject is counted only once regardless of the number of events or the number of occurrences.

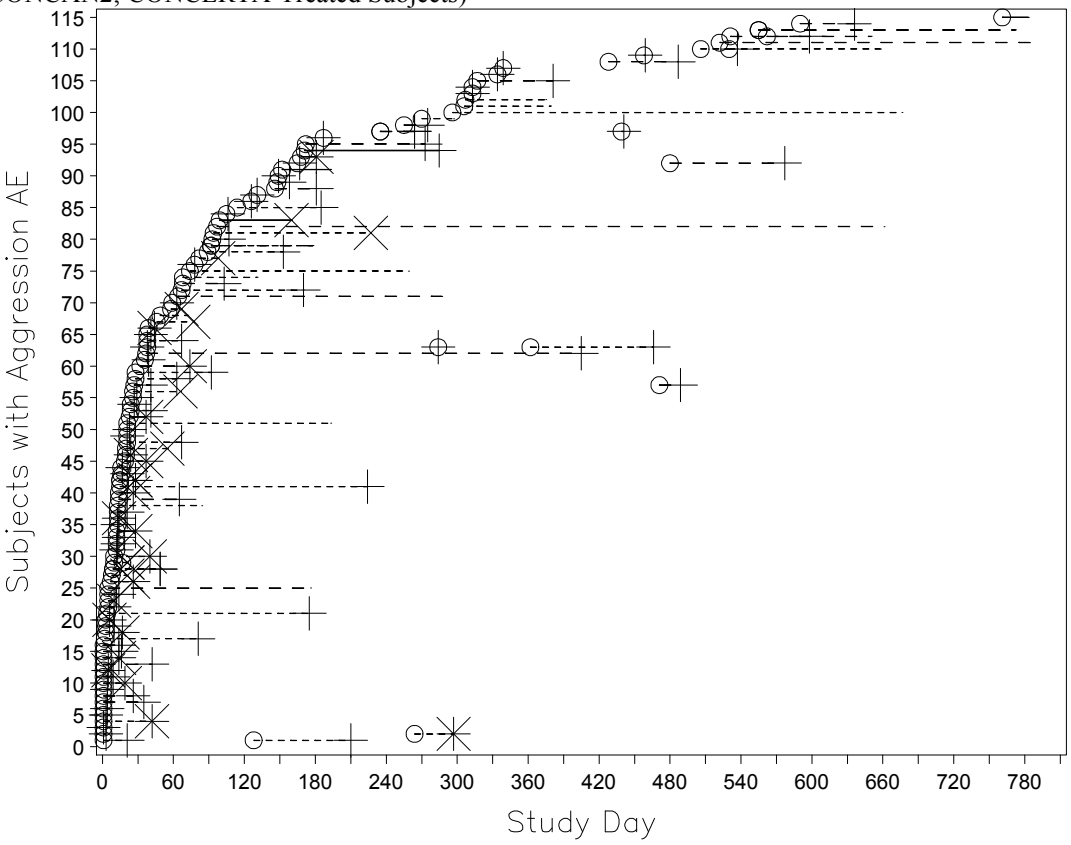
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was established for Anger. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Table 54: Important Identified Risk: Aggression (Continued)

Onset and Duration of Aggression: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750	780	810
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)	17 (1)	10 (1)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

— — — — — — · Mild
---------- Moderate
———— Severe

o Start of Event
- Persisting
+ Resolved
X Drug Withdrawn

Table 54: Important Identified Risk: Aggression (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Aggression Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of Events	
Important Identified Risk	**Nonserious[a]**	**Serious[a]**
Aggression	2,201	693

[a] At event level

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for this risk are provided in Annex 5.

Background incidence/prevalence	An estimated 20% to 40% of children with ADHD will develop conduct disorder, which can be characterised by aggressive behaviour toward people, animals, or property.[a] At baseline in the MTA study, 14.7% of children with ADHD suffered from conduct disorder. At the 14-month follow up, the prevalence decreased to 7.2%, with no significant differences observed between treatment groups.[b] Similarly, at the 6-year follow up no significant differences were observed for mean scores of aggression and conduct based on DSM-IV symptoms of conduct disorder between treated or untreated groups.[c]
Risk groups or risk factors	Rates of certain comorbid psychiatric conditions associated with aggressive behaviour are higher in ADHD patients. For example, one study found the odds ratios for the comorbid conditions of oppositional defiant disorder and conduct disorder to be 17.7 and 5.5, respectively, in children with ADHD relative to the general population of children.[d]
Potential mechanisms	ADHD is a collection of symptoms, ie, inattention, impulsivity and hyperactivity, which can occur in conjunction with other mental health conditions. Aggression is a common symptom in paediatric psychiatric disorders. As such, aggressive behaviour probably reflects a common developmental trajectory frequently expressed in children and adolescents who are diagnosed with any psychiatric disorder, rather than being a specific symptom of ADHD.[e] The mechanism by which CONCERTA may have a role in the occurrence or worsening of aggression has not been determined.
Preventability	Education of caregivers, prescribers, early detection and management of risk factors and symptoms. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent.
Potential public health impact of safety concern	Aggression has been reported in the clinical database. Since drug-induced aggression is reversible upon discontinuation of methylphenidate, should it occur, it is not anticipated to have a significant public health impact.
Regulatory action taken	European Union: The core methylphenidate SmPC updated (in UK/H/PSUR/0068/001) this wording to add "upwards or downwards titration may be appropriate. Treatment interruption can be considered".

Key: Attention Deficit Hyperactivity Disorder, SmPC=Summary of Product Characteristics

a: National Institute of Mental Health (NIMH) (2004). Bethesda (MD): US Department of Health and Human Services; 2004 Attention Deficit Hyperactivity Disorder. http://www nimh.nih.gov/publicat/ NIMHadhdpub.pdf. Accessed on April 24 2007.

b: Hechtman L (2005), Etcovitch J, Platt R, et al. Does multimodal treatment of ADHD decrease other diagnoses? *Clin Neurosci Res* 2005;5(5):273-282.

c: Molina BSG (2009), Hinshaw SP, Swanson JM, et al. MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500

d: Guevara J (2002), Lozano P, Wickizer T, Mell L, Gephart H. Psychotropic medication use in a population of children who have attention deficit/hyperactivity disorder. *Pediatrics* 2002;109(5):733-739

e: Tauscher-Wisniewski S (2006). Aggression in attention-deficit/hyperactivity disorder children: diagnostic or comorbid symptom? *Expert Rev Neurotherapeutics* 2006;6:197-199.

Table 55: Important Identified Risk: Depression

Identified Risk: Depression*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	4 (1.2)	226 (8.3)
vs	VS	
Placebo (N=318)	4 (1.3)	
Odds Ratio	1.0	NA
95% confidence interval***	0.2 to 5.4	
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	4
Discontinued Treatment	1	44
Resolved/Recovered/Recovered From AE	2	114
Recovered With Residual Effects	0	3
Continuing/Not Yet Recovered	1	87
Severity****		
Mild	3	108
Moderate	1	98
Severe	0	18

* MedDRA preferred terms searched for this risk are provided in Annex 5.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Depression. The subject is counted only once regardless of the number of events or the number of occurrences.

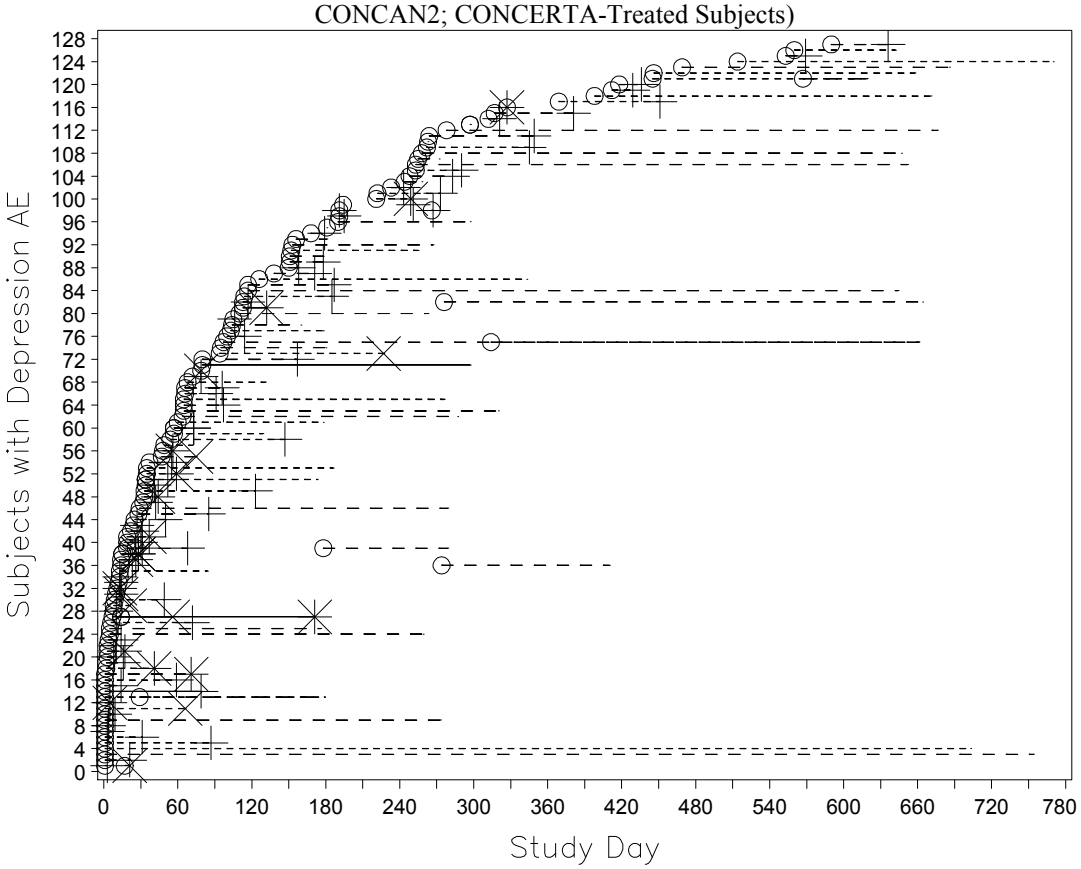
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was established for Depression. A causal relationship was not established for any other adverse event that may be relevant for this important identified risk.

Table 55: Important Identified Risk: Depression (Continued)

Onset and Duration of Depression: Open-Label Trials of at Least 3 Months (C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750	780
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)	17 (1)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

Table 55: Important Identified Risk: Depression (Continued)

Postmarketing

Cumulative Count of Events for the Important Identified Risk of Depression Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of Events	
Important Identified Risk	**Nonserious[a]**	**Serious[a]**
Depression	2,009	418

[a]At event level

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for these risks are provided in Annex 5.

Background Incidence/ Prevalence	In one series of studies, the lifetime prevalence of severe depression among children with ADHD (280 subjects) was 15% in girls and 29% in boys compared with 1% to 2% of boys and girls without ADHD. [a] An increased risk for major depression in children and adolescents with ADHD has been consistently reported in the medical literature.[b] Epidemiologic studies have reported that comorbid depression may be found in roughly 20% to 30% of ADHD cases.[c] The MTA was a NIMH US-sponsored clinical study of 579 children (ages 7-10 years) with ADHD. At baseline assessment, 3.8% of the ADHD subjects were found to have major depression, as measured by parent and teacher responses. This represents an elevated prevalence in comparison to the general population estimate of 2.5% for that age group.[d]
Risk groups or risk factors	When assessing the background risk (independent of drug), depression in patients with ADHD is complex and not well understood. Both a family (ie, genetic) as well as a disease component may be possible.
Potential mechanisms	CONCERTA® is known to increase dopamine and norepinephrine in the interneuronal space. Both of these neurotransmitters have important roles in the aetiology of certain psychiatric disorders including mood disorders.
Preventability	Early detection, appropriate diagnosis and management including timely pharmacotherapy and psycho-therapy to prevent relapses; education of prescribers, patients, and caregivers. Careful monitoring of patients for adverse events, especially early on in treatment, is prudent.
Potential public health impact of safety concern	Depression itself does impact public health. However, in methylphenidate clinical trials, the frequency of depressive symptoms in patients with ADHD was not substantially higher than that expected in an ADHD population. Based on the available evidence, no impact of methylphenidate-induced depression on public health is expected.
Regulatory action taken	European Union: Amendments were made to the SmPC following an Article 31 referral procedure for methylphenidate in the EU which concluded on 27 May 2009: This includes pre-treatment screening and ongoing monitoring recommendations at Section 4.2 and Section 4.4 of the SmPC.

Key: ADHD=Attention Deficit Hyperactivity Disorder, EU=European Union, SmPC=Summary of Product Characteristics

a: Fishman PA, Stang PE, Hogue SL. Impact of comorbid attention deficit disorder on the direct medical costs of treating adults with depression in managed care. *J Clin Psychiatry* 2007;68(2):248-253

b: Biederman J, Mick E, Faraone SV. Depression in attention deficit hyperactivity disorder (ADHD) children: "True" depression or demoralization? *J Affective Disorder* 1998;47:113-122

c: Anderson JC, Williams S, McGee R, Silva PA. DSM-III disorders in preadolescent children. Prevalence in large sample from the general population. *Arch Gen Psych* 1987;44(1)69-76

d: Jensen PS, Hinshaw SP, Kraemer HC, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. *J Am Acad Child Adolesc Psychiatry* 2001;40(2):147-158

Important Potential Risks

The potential risks listed below represent the current list of potential risks in the Core Table of Risks for methylphenidate-containing products. Of these important potential risks, a causal relationship with OROS methylphenidate HCl was established for Tics.

- Migraine
- Repetitive behaviours
- QT prolongation
- Cyanosis
- Arrhythmias
- Sudden death
- Ischaemic cardiac events
- Cerebrovascular disorders
- Hostility
- Suicidality
- Tics/Tourette's syndrome/Dystonias
- Effect on final height
- Sexual maturation (delayed)
- Carcinogenicity
- Off-label use
- Diversion
- Withdrawal syndrome
- Drug abuse and drug dependence
- Lymphocytic leukaemia
- Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory
- distress/apnoea)
- Neonatal effects on growth

Table 56: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias

Potential Risk: Tics/Tourettes's Syndrome/Dystonias*	All Randomised, Blinded Trials Population (N=321) N (%)	All Clinical Trials Population (N=2718) N (%)
Frequency**		
Concerta®	1 (0.3)	92 (3.4)
vs	VS	
Placebo (N=318)	5 (1.6)	
Odds Ratio	0.2	NA
95% confidence interval***	0.0 to 1.8	
Seriousness/outcomes****		
Resulted in Death	0	0
Was Serious	0	0
Discontinued Treatment	0	24
Resolved/Recovered/Recovered From AE	1	45
Recovered With Residual Effects	0	2
Continuing/Not Yet Recovered	0	42
Severity****		
Mild	1	49
Moderate	0	38
Severe	0	5

* MedDRA preferred terms searched for this risk are provided in Annex 5.

** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Tics/Tourettes's syndrome/Dystonias. The subject is counted only once regardless of the number of events or the number of occurrences.

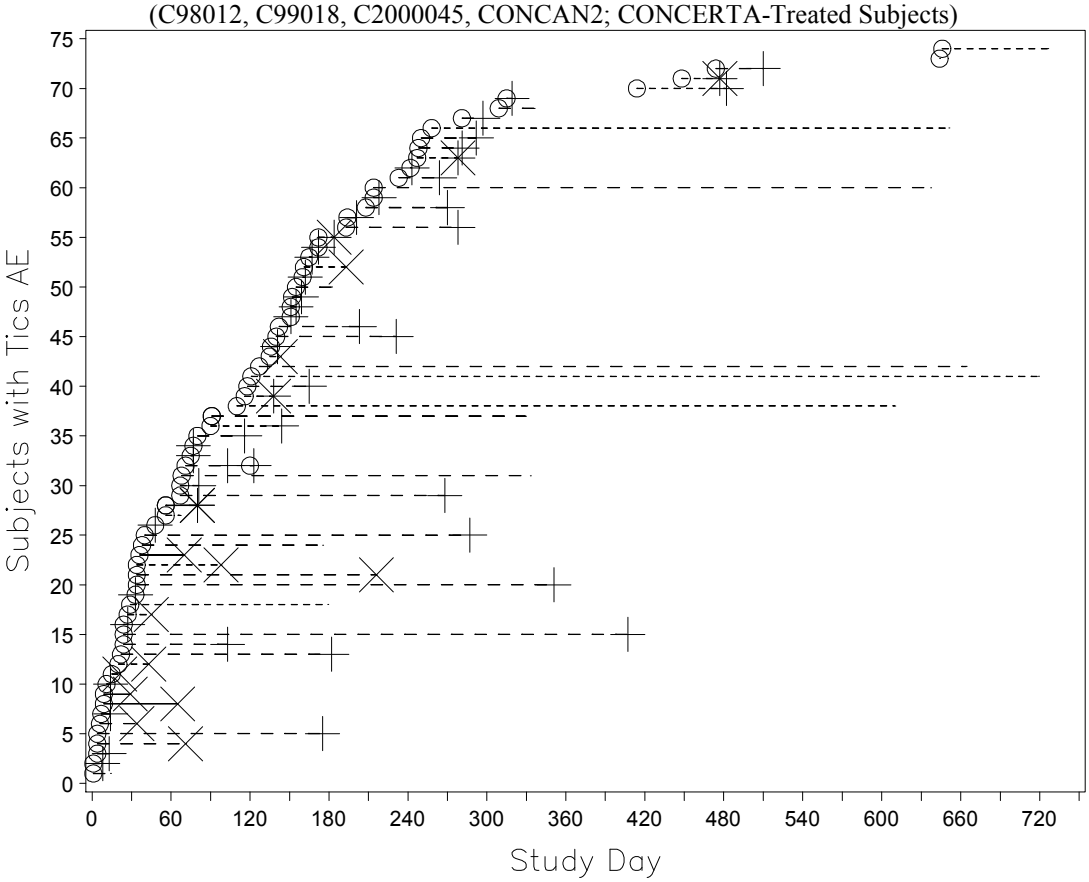
*** The 2-sided exact 95% CI in odds ratio is of CONCERTA® to the comparator.

**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

On the basis of the review of aggregate safety data from clinical trials of OROS methylphenidate HCl, a causal relationship was established for Tic.

Table 56: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Onset and Duration of Tics, Tourette's Syndrome, Dystonias: Open-Label Trials of at Least 3 Months
(C98012, C99018, C2000045, CONCAN2; CONCERTA-Treated Subjects)



Day	0	30	60	90	120	150	180	210	240	270	300	330	360
N (%)	1583 (100)	1484 (94)	1386 (88)	1308 (83)	1255 (79)	1232 (78)	1152 (73)	1070 (68)	1034 (65)	809 (51)	396 (25)	345 (22)	296 (19)

Day	390	420	450	480	510	540	570	600	630	660	690	720	750
N	274 (17)	269 (17)	265 (17)	261 (16)	256 (16)	252 (16)	244 (15)	242 (15)	214 (14)	132 (8)	86 (5)	60 (4)	37 (2)

* For Trial C2000045, only subjects who remained in the trial beyond 21 days and who consequently could have been exposed to trial drug for a period up to 12 months were included in the analysis.

— — — — — — · Mild
---------- Moderate
———— Severe

o Start of Event
\- Persisting
\+ Resolved
X Drug Withdrawn

(Continued)

Table 56: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Postmarketing

Cumulative Count of Events for the Important Potential Risks of Tics, Tourette's syndrome and Dystonia Reported at Least Once Between 01 August 2000 and 10 October 2012 by Seriousness

	Number of Events	
Important Potential Risks	**Nonserious[a]**	**Serious[a]**
Tics, Tourette's Syndrome, Dystonia	583	257

[a] At event level

Source: Global Medical Safety database (SCEPTRE). MedDRA preferred terms searched for these risks are provided in Annex 5.

Background incidence/prevalence	All children aged 5 to 15 years in the county of Varmland (central Sweden) who had a diagnosis of Tourette's syndrome from 1 January 1995 through 30 June 1998 were examined with regard to clinical symptoms, severity, and comorbidity. Of 58 children diagnosed with Tourette's syndrome, there was a very high rate of comorbid ADHD (64%).[a] There have been few epidemiological studies of dystonia. Most previous studies have provided estimates based on few cases. A European prevalence study was undertaken to provide more precise rates of dystonia by pooling data from 8 European countries. Diagnosed cases of dystonia were ascertained by adult neurologists working in specialist movement disorder (and botulinum toxin) clinics. The crude annual period prevalence rate (1996-1997) for primary dystonia was 152 per million (95% confidence interval 142-162), with focal dystonia having the highest rate of 117 per million.[b]
Risk groups or risk factors	ADHD and tic disorders, including Tourette's syndrome, are common disorders of childhood, with ADHD affecting 4 to 10% of school age children in the US and Tourette's syndrome affecting 1 to 3%.[c] The occurrence of tics in special education classes in the US has been reported as high as 25%.[d,e,f] Stimulants, the recognised first-choice of pharmacotherapy for ADHD, carry a warning in the US label that they should not be used in children with a prior history of tics or a family history of Tourette's syndrome. New studies have been conducted and existing data analysed to better understand the appropriateness of the use of methylphenidate in 2 co-existing, co-morbid disorders. Palumbo and colleagues (2004) analysed data from 5 trials (2 placebo-controlled, active controlled and 3 open label), which lasted from 1 to 4 weeks to 2 years.[g]
Potential mechanisms	Movement disorders such as tics are believed to have a dopaminergic component. CONCERTA® is known to increase dopamine in theinterneuronal space. The specific pathways that are responsible forstimulant-induced tics have not been elucidated. The data from open-label trials indicate that the incidence of tics in the treated population does not exceed the background incidence. Although the issues are difficult to separate, the development of tics is believed to primarily be from the disease state, and not the treatment.
Preventability	Tourette's syndrome - timely and accurate diagnosis, education, and behaviour or pharmacologic interventions (neuroleptics and dopamine receptor antagonists). Tics and dystonias - timely and accurate diagnosis, pharmacotherapy (dopamine receptor blocking agents). Family history should be assessed.

Table 56: Important Potential Risk: Tics, Tourette's Syndrome, Dystonias (Continued)

Potential public health impact of safety concern	A comprehensive evaluation for tics should be performed prior to starting any therapy. The long-term outcome is generally favourable. Nevertheless, movement disorders may result in a moderate to severe level of functional impairment in school-age children. The data from open-label trials indicate that the incidence of tics in the treated population does not exceed the background incidence; however, it is higher in the ADHD diagnosed population. This is not expected to rise to the level of a public safety concern.
Regulatory action taken	European Union: None

Key: ADHD=Attention Deficit Hyperactivity Disorder,

a: Kadesjo B, Gillberg C. Tourette's disorder: epidemiology and comorbidity in primary school children. *J Am Acad Child Adolesc Psychiatry* 2000;39(5):548-555.

b: Epidemiological Study of Dystonia in Europe Collaborative Group (ESDE). A prevalence study of primary dystonia in eight European countries. *J Neurol* 2000;247(10):787-792.

c: American Academy of Pediatrics (AAP 2000). Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder. *Pediatrics* 2000;105:1158-1170

d: Comings DE, Himes JA, Comings BG. An epidemiologic study of Tourette's Syndrome in a single school district; 1990. *J Clin Psychiatry* 51(11):463-469.e:

e: Kurlan R, Whitmore D, Irvine C, McDermott MP, Como PG. Tourette's syndrome in a special education population: A pilot study involving a single school district. *Neurology* 1994;44(4)699-702

f: Mason A, Barnerjee S, Eapen V, Zeitlin H, Robertson MM. The prevalence of Tourette's syndrome in a mainstream school population. *Dev Med Child Neurol* 1998;4(5):292-296.

g: Palumbo D, Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. *J Child Adolesc Psychopharmacol* 2004;14(2):185-194

16.5. Effectiveness of Risk Minimisation

For all the important identified and potential risks described in Section, 16.1, appropriate labelling changes have been made as part of routine risk minimisation efforts.

As part of the EU Article 31 referral conditions, the MAHs for methylphenidate products developed an additional risk minimisation measure to educate physicians on the use of methylphenidate in accordance with the safety guidance given in the safety sections of the core European Union methylphenidate SmPC. See the Regional Appendix for an update of this additional risk minimization tool during this period.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy/Effectiveness Information

CONCERTA® (OROS methylphenidate hydrochloride) is indicated for the treatment of ADHD in children 6 years of age and older, adolescents, and adults up to the age of 65.[142]

A diagnosis of ADHD (according to the Diagnostic and Statistical Manual, Edition V [DSM-5]) requires the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 12 years. The symptoms must cause clinically significant

[142] Janssen Research and Development, LLC. CONCERTA® Company Core Data Sheet; 15 May 2012.

impairment, eg, in social, academic, or occupational functioning, and be present in 2 or more settings, eg, school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met. For adults, a lower threshold (5 instead of 6 symptoms) is sufficient for a reliable diagnosis.

The place of methylphenidate in the treatment of ADHD is well established. The international birth date of OROS methylphenidate HCl is 01 August 2000 based on the product's first approval in the US. OROS methylphenidate HCl has additionally been authorized for use in children, adolescents, and adults (up to 65 years of age) with ADHD in a number of countries since 2008.

OROS methylphenidate HCl prolonged-release tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg tablets. The dosage may be adjusted in 18 mg increments at weekly intervals to a maximum of 72 mg/day in children/adolescents and 108 mg/day in adults, and should be individualized according to subject need and response.

The efficacy of OROS methylphenidate HCl has been assessed for each of the indications listed in the CCDS (15 May 2012). The studies that were used in the baseline benefit-risk evaluation for OROS methylphenidate HCl are summarized below.

Children/Adolescents

This indication was established at first registration in the United States on 01 August 2000; 4 pivotal, controlled studies and 2 uncontrolled studies in subjects beginning OROS methylphenidate HCl treatment form the basis for approval.[143] Two long-term studies are also discussed to support the maintenance of effect.

Controlled Studies

C-98-003

This was a single-centre trial with a screening and practice day followed by a double-blind, randomized crossover comparison of OROS methylphenidate HCl once daily, Ritalin® IR (methylphenidate) 3 times daily, and placebo. A total of 64 subjects (52 males and 12 females) aged 6 to 12 received all 3 treatments in random order. OROS methylphenidate HCl was given as a single daily dose in the morning and methylphenidate was given in three divided daily doses, in the morning, at mid-day, and after school. Each patient was assigned to 1 of 3 dosage levels of OROS methylphenidate HCl or methylphenidate depending on their previous dose of methylphenidate. The dosage groups were OROS methylphenidate HCl 18 mg daily or 15 mg methylphenidate per day, OROS methylphenidate HCl 36 mg or methylphenidate 30 mg per day, and OROS methylphenidate HCl 54 mg or methylphenidate 45 mg per day. Subjects received each treatment for 1 week. The primary efficacy rating was the IOWA Conners Rating Scale (intattention/overactivity [I/O] subscale). This was elicited by the community school teacher at Days 6, 13, and 20. The secondary endpoint was the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) combined attention scale at 1, 2, 3, 5, 7, 9, 10, 11, and 12 hours after administration of study medication on Days 7, 14, and 21.

The analysis demonstrated that OROS methylphenidate HCl was significantly more effective than placebo ($p<0.001$) and no differences between OROS methylphenidate HCl once daily and methylphenidate 3 times daily were found. Examples of the actual IOWA Conners assessment scores (I/O) as assessed at school were 6.66 with OROS methylphenidate HCl, 7.1 with methylphenidate 3 times daily and 11.6 with placebo, confirming the appropriate clinical benefit with OROS methylphenidate HCl. The onset and duration of efficacy (assessed with SKAMP) was estimated between 1 to 2 hours and continued through 12 hours for both the OROS methylphenidate HCl and methylphenidate treatments. The result with OROS methylphenidate HCl was statistically different from placebo ($p<0.005$) and similar to methylphenidate. The degree of change in SKAMP scales (of 1 to 2 point improvement) was similar for both active treatment groups and in line with the expected clinical benefit from methylphenidate therapy. Actigraph data demonstrated that, during the classroom periods, activity of subjects was lower on the OROS methylphenidate HCl and methylphenidate treatments than on placebo. In global assessments, efficacy in the home, community school, and laboratory school environments were rated as good or excellent for the OROS methylphenidate HCl and methylphenidate treatments more frequently than the placebo treatment. Furthermore, subjects demonstrated higher academic productivity (increased ability to complete math

[143] Johnson & Johnson Research & Development. Module 2.5 Clinical Overview, CONCERTA® 18 July 2007.

problems in a given time) during the OROS methylphenidate HCl and methylphenidate treatments than during the placebo treatment. The investigators concluded that the improved performance on objective tests for subjects given OROS methylphenidate HCl applied to those who had already benefited from methylphenidate treatment. This was reasonable given the duration, design, and purpose of the study.

C-97-025

This was a randomized, double-blind (DB) crossover trial evaluating the efficacy and safety of OROS methylphenidate HCl, methylphenidate, and placebo in 62 males and 8 female subjects aged from 6 to 12 years with ADHD with 1 week on each treatment. The trial had essentially the same design and dosage levels as C-98-003. However, the study was conducted using the early bilayer formulation of the OROS methylphenidate drug delivery system, which has been shown to be bioequivalent to OROS methylphenidate HCl. The analysis demonstrated that OROS methylphenidate HCl was significantly more effective than placebo ($p<0.001$) and no differences between OROS methylphenidate HCl once daily and methylphenidate 3 times daily were found. Actual I/O subscale scores as assessed at school were 4.7 with OROS methylphenidate HCl, 5.0 with methylphenidate 3 times daily, and 10.4 with placebo, confirming the appropriate clinical benefit with OROS methylphenidate HCl. Using the SKAMP rating scale, both OROS methylphenidate HCl and methylphenidate demonstrated onset of efficacy at 1.5 hours after the morning dose with efficacy continuing through 12 hours after the first dose. In addition, subjects demonstrated higher academic productivity and greater accuracy during the OROS methylphenidate HCl and methylphenidate treatments than during the placebo treatment. Conclusions similar to those from Trial 98-003 were made by the investigators; specifically, that the benefits of OROS methylphenidate HCl applied to those subjects who had previously responded to the methylphenidate.

C-98-005

This was a multicentre, DB, parallel-group, double-dummy, randomized trial comparing the efficacy and safety of OROS methylphenidate HCl, methylphenidate, and placebo in 312 children (259 male and 53 female) children with ADHD for 28 days. Subjects were assigned to 1 of 3 treatment dose levels (18 mg, 36 mg, and 54 mg once daily for OROS methylphenidate HCl, and 5 mg, 10 mg, and 15 mg given 3 times daily for methylphenidate) based on their dosage regimen immediately prior to trial inclusion. The primary endpoint was to test the null hypothesis that the treatment difference between OROS methylphenidate HCl and placebo, as measured on the community school teacher IOWA Conners Rating Scale assessment for last evaluation of each subject, was zero. Seventy-one subjects prematurely discontinued the investigation. Fifty-nine discontinued early because of lack of efficacy; 38, 11, and 10 patients in the placebo, the OROS methylphenidate HCl and the methylphenidate groups, respectively. Twelve subjects discontinued because of non-compliance. Results indicated that OROS methylphenidate HCl given once a day was significantly more effective than placebo and similar to methylphenidate 3 times daily in the treatment of ADHD. Actual IOWA I/O subscale scores as assessed at school were 6.0 with OROS methylphenidate HCl, 6.4 with methylphenidate 3 times daily, and 9.8 with placebo, confirming appropriate clinical benefit with OROS methylphenidate HCl. Consistent results

were obtained from different assessors (community school teacher, parent/caregiver, and investigator) and in different settings (at community school, school, and home). The effectiveness of both treatments in improving attention and behaviour in ADHD subjects was apparent at first assessment after 1 week of treatment in both the community school and home settings and persisted throughout the 28-day trial period.

This trial was significant in that it confirmed the essential efficacy of OROS methylphenidate HCl due to the lack of confounding factors which may occur in crossover studies and because of the longer assessment of efficacy. From the numbers of drop-outs due to lack of efficacy with placebo (38 total), longer-term comparative studies are likely to be impractical.

01-146

The efficacy of OROS methylphenidate HCl at doses of up to 72 mg/day in adolescents is supported by the results of a double-blind placebo-controlled study in adolescents with ADHD.[144] Study 01-146 consisted of 4 phases: 1-week washout phase; 1- to 4-week open-label dose-titration phase; 2-week double-blind placebo-controlled phase; and 8-week open-label follow-up phase during which safety was assessed. During the dose-titration phase, treatment was initiated with one 18 mg tablet of OROS methylphenidate HCl daily. The dose was increased in 18 mg increments approximately every 7 days (± 2 days) to a maximum of 72 mg daily until an individualized dose was identified. Subjects were then randomised to receive either their individualized OROS methylphenidate HCl dose or a matched placebo for the 2-week double-blind phase. Five different rating scales were then used to assess improvements in ADHD symptoms over this period. The ADHD Rating Scale (ADHD-RS) was employed as the primary efficacy measure. The secondary measures of efficacy were: 1) parent assessment using the ADHD-RS; 2) subject self-assessment using the Conners-Wells' Self-Report Scale, 3) the Child Conflict Index, 4) the investigator-rated Clinical Global Impression of Improvability (CGI-I), and 5) the Global Assessment of Efficacy (GAE). During the course of the double-blind phase, 25% of subjects withdrew and the attrition rate was higher in the placebo group than the OROS methylphenidate HCl group (31% vs. 18%). The primary reason for attrition was a perceived or real lack of efficacy. Discontinuation from the double-blind phase may have been biased by the knowledge that patients who discontinued early could enter the open-label phase of the study. This could have decreased the apparent response and the difference between medication and placebo.

The efficacy of OROS methylphenidate HCl at each subject's individualised dose (ie, the dose – 18 mg/day, 36 mg/day, 54 mg/day or 72 mg/day – which achieved a pre-specified level of improvement in ADHD symptoms in a patient) was assessed relative to placebo in a 2-week double-blind placebo-controlled phase of the study. Both clinically and statistically significant improvements over baseline were seen in the primary and all secondary efficacy endpoints during the placebo-controlled phase of the study for OROS methylphenidate HCl compared with placebo, thus indicating the efficacy of OROS methylphenidate HCl doses between 18 and

[144] Johnson & Johnson Pharmaceutical Research & Development. Module 2.5 Clinical Overview, CONCERTA® (Prolonged Release Tablets 18 mg, 36 mg, 54 mg, Type II Variation – Addition of 72 mg daily dose for Adolescents. 23 July 2004. EDMS-PSDB-3209665:2.0.

72 mg/day in adolescents. Significant improvements in symptoms were apparent to investigators, parents, and subjects themselves. For all efficacy parameters, the change from baseline to the end of the double-blind phase for the 72 mg dose group was similar to that achieved in the other dose groups. These data thus support the efficacy of OROS methylphenidate HCl 72 mg once-daily in adolescents with ADHD who do not achieve sufficient symptom control at lower OROS methylphenidate HCl dose levels.

Uncontrolled Studies

C-98-007

This investigation was a multicentre, open-label, non-randomized, dose-escalation trial in 111 subjects who had not been taking methylphenidate. The dose-escalating scheme used required that all subjects start OROS methylphenidate HCl at 18 mg once daily. The dose was increased by 18 mg at weekly intervals until a safe and effective dose was identified, to a maximum dose of 54 mg once a day. Dosing was continued up to 3 weeks. Effectiveness was evaluated weekly in the community setting by school teachers and parents/caregivers and by the investigator using standardized behaviour scales and other assessments. Of 111 subjects entered into the trial, 95 subjects were titrated to a successful dose that was considered to be safe and effective by the investigator. The majority of subjects (54.7%) required a final dose of 36 mg once daily, with 26% receiving 54 mg. In this trial, the effective dose appeared related to weight and height. Younger subjects were more likely than the 10 to 12 year olds to respond to 18 mg once daily. However, 36 mg once daily was the most effective dose across various age groups. The trial supports the starting dose of 18 mg of OROS methylphenidate HCl for methylphenidate naïve subjects, which is comprised of approximately 4 mg of immediate release and 14 mg of controlled release methylphenidate.

Long-Term Maintenance Studies (Children)

The long-term efficacy of OROS methylphenidate HCl treatment in children/adolescents is supported by the following 2 trials:

- Study C-98-012 was a multicentre, open, long-term trial of safety in 432 children (361 males, 71 females) aged 6 to 13 years followed monthly for up to 1 year. Subjects were treated with 18 mg, 36 mg, or 54 mg, and they moved to higher dosages when clinically indicated. A total of 222 subjects (51.4%) completed the study, with 106 subjects (47.7%) progressing to the highest dose. At the highest dose level, a total of 36 subjects (18.2%) were discontinued due to lack of efficacy. In the lower dosage groups, there was only 1 drop out (36 mg dose level). The results of this trial confirmed that the efficacy of OROS methylphenidate HCl in treating ADHD was maintained over monthly follow-up visits.
- A multicentre, open-label, non-randomized, single-treatment trial was conducted in 407 children aged 6 to 13 years who previously participated in short-term, controlled studies of once-daily OROS methylphenidate HCl without significant drug-related adverse events.[145] Children were assigned to 1 of 3 dosage levels (18 mg, 36 mg, or 54 mg once

[145] Wilens T, McBurnett K, Stein M, et al. ADHD treatment with once-daily OROS methylphenidate: Final results from a long-term open-label study. *J Amer Acad Child Adolesc Psychiatry*, 2005; 44(10):1015-1023.

daily), based upon their dose in a previous controlled study, for up to 24 months. Doses could be adjusted between levels as appropriate, and subjects were permitted to stop taking OROS methylphenidate HCl on weekends or non-school days, and to take medication holidays. Efficacy was assessed by parents, teachers, and investigators using established rating scales every 3 months. Out of the 407 children who enrolled in the study, 289 (71%) completed 12 months, 179 (44%) completed 21 months, and 56 (14%) completed 24 months of the study. Global assessments of efficacy obtained though ADHD rating scales indicated that OROS methylphenidate HCl demonstrated efficacy throughout the study.

Adults

Three Phase 3 studies formed the basis for the adult indication using OROS methylphenidate HCl to treat ADHD in those subjects whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.[146] Additional long-term studies support the maintenance of effect.

3002-DB

This trial was a multicentre, double-blind, randomized, placebo-controlled, parallel-group, dose-response trial (5-week duration) with 3 fixed-dose groups (18, 36, and 72 mg).[147] Subjects were randomized to receive OROS methylphenidate HCl administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). Ninety-one percent of subjects completed the study with adverse events being the most common reason for early withdrawal. Less than 3% of drop-outs were attributed to a lack of efficacy. OROS methylphenidate HCl demonstrated statistically significant and clinically relevant superiority to placebo with regard to changes from baseline to double-blind end point in the Connors Adult ADHD Rating Scale (CAARS) ADHD symptoms total score. The improvement was first observed at Week 1 (first assessment timepoint) for all doses, and statistical superiority over placebo was maintained throughout the 5-week, double-blind phase (except that the difference between 18 mg and placebo was not statistically significant at Week 3). The significant findings of the primary efficacy variable were supported by significant improvements relative to placebo for all 3 doses for most secondary efficacy variables, including functional outcome as reflected in the Sheehan Disability Scale (SDS) total score and responder rate based on the primary efficacy variable. A post hoc analysis based on all randomized subjects confirmed the results of the analysis of the primary efficacy variable based on the intent-to-treat population.

02-159

This trial demonstrated the effectiveness of OROS methylphenidate HCl in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final trial visit on the Adult ADHD Investigator Rating Scale (AISRS).

[146] Johnson & Johnson Pharmaceutical Research & Development. Module 2.5 Clinical Overview, CONCERTA® for the treatment of adults with attention deficit hyperactivity disorder (ADHD). 30 December 2009. EDMS-PSDB 10822217:2.0

[147] Wilens T, McBurnett K, Stein M, Lerner M, Spencer T, Wolraich M. ADHD treatment with once-daily OROS methylphenidate: Final results from a long-term open-label study. *J Amer Acad Child Adolesc Psychiatry*, 2005; 44(10):1015-1023

Of 226 subjects who entered the 7-week trial, 110 were randomized to OROS methylphenidate HCl and 116 were randomized to placebo. Treatment was initiated at 36 mg/day and subjects continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. Seventy-one percent of subjects completed the study with adverse events being the most common reason for early withdrawal. Less than 3% of drop-outs were attributed to a lack of efficacy. Mean changes from baseline at double-blind end point in the clinician-rated AISRS total score were statistically significant and clinically relevant for OROS methylphenidate HCl compared with placebo. In addition, OROS methylphenidate HCl was statistically significantly superior to placebo for key secondary efficacy variables such as CGI-I score at end point, change in CAARS - Self Report: Short Form total score, and responder rate. By virtue of a pre-defined step-down procedure that controlled the overall Type I error rate, OROS methylphenidate HCl showed greater improvement, but not a statistically significant difference, for other secondary efficacy variables, including functional outcomes such as the SDS work subscale score and the ADHD Impact Mobile-Adult (AIM-A) work/home/school domain score.

3013

A multi-centre, double-blind, placebo-controlled, dose-titration study lasting up to 13 weeks was conducted in adults with ADHD. A total of 279 subjects aged 18 to 65 years old with a chronic course of ADHD starting prior to age 7 years were randomized to placebo (N=97) or OROS methylphenidate HCl (54 mg [n=90] or 72 mg [n=92]). After a 5-week titration phase, treatment continued for 2 weeks for a maximum of 51 days of treatment. Treatment with a maintenance dose lasted from 2 to 6 weeks, depending on how quickly the subject met their individualized dose. Sixty-four percent of subjects completed the study with adverse events being the most common reason for early withdrawal. In total, 7% of drop-outs were attributed to a lack of efficacy (placebo: 14 drop-outs; 54 mg: 1 drop-out, 72 mg: 4 drop-outs). In this trial, OROS methylphenidate HCl 72 mg was statistically significantly superior to placebo in reducing the CAARS ADHD symptoms total score from baseline to double-blind end point. Improvement was first observed at Week 3 (first assessment timepoint after titration to assigned dose), and statistical superiority over placebo was maintained throughout the 13-week, double-blind trial. The significant findings of the primary efficacy variable were supported by significant improvements for the 72 mg group relative to placebo for most secondary efficacy variables, including the Clinical Global Impression - Severity (CGI-S) and CGI-I scores, AIM-A work/home/school performance and daily functioning domain score, and responder rate based on the primary efficacy variable. Changes from baseline in the SDS total score at double-blind end point did not differ between the 72 mg and placebo groups. The difference between the 54 mg group and the placebo group for the primary efficacy variable and many secondary variables was not statistically significant for the analysis involving the intent-to-treat population. When the primary analysis was repeated using the modified intent-to-treat population (which excluded subjects who discontinued due to reasons other than lack of efficacy) and the per-protocol population (which excluded subjects with major protocol deviations), these analyses showed statistically significantly larger decreases from baseline to double-blind end point in the CAARS ADHD symptoms total score for both the 54 and 72 mg groups relative to the placebo group.

Long-Term Maintenance Studies (Adults)

At the time of first registration, data documenting the long-term course of ADHD treatment with OROS methylphenidate HCl in adults was lacking. However, documentation of the maintenance of effect for other methylphenidate-containing products was well-established. Since approval, the following long-term trials using OROS methylphenidate HCl have provided additional evidence supporting long-term use:

- In Trial 3004-OL (an extension phase of Trial 3002-DB), 155 subjects aged 18 to 65 were treated with OROS methylphenidate HCl (18 to 90 mg/day) for up to 2 years. A total of 99 subjects completed the study, with 3 dropping out due to a lack of efficacy. All efficacy parameters showed improvement at open-label end point compared to baseline, and the improvement from baseline was statistically significant for many variables, including the investigator-rated CAARS scale. There was no evidence suggestive of the development of tolerance to the therapeutic benefits of OROS methylphenidate HCl with continued treatment for up to 2 years.
- Trial 12-304 was a multi-centre, open-label, dose-titration, long-term safety study in adult subjects diagnosed with chronic, symptomatic ADHD from childhood conducted in the United States. Subjects enrolled during the first 3 months of the study were assigned to a 1-year duration; subjects enrolled after this time were assigned to a 6-month duration. Subjects who completed Trial 02-159 (randomized, double-blind, placebo-controlled study) could also be enrolled into Trial 12-304. A total of 560 subjects (aged 18 to 65) were enrolled, of which 550 subjects were evaluable for safety and efficacy; 258 subjects consented to the 6-month study period and 292 subjects consented to the 12-month study period. Of the evaluable subjects, 15% (84 subjects: 38 OROS methylphenidate HCl and 46 placebo during double blind treatment) previously participated in Study 02-159. Individualized doses of OROS methylphenidate HCl ranging from 36 to 108 mg/day were administered. Subjects taking OROS methylphenidate HCl demonstrated improvement in all efficacy evaluations (AISRS and Global Assessment of Functioning [GAF] scores) performed.

17.2. Newly Identified Information on Efficacy/Effectiveness

Company-Sponsored Trial

Adults

The OROS methylphenidate HCl Quality of Life (CONQoL) trial (42603ATT4053), a 12-week, multicentre, open-label trial, assessed the effectiveness of OROS methylphenidate HCl on QoL variables in 60 Brazilian subjects (18 to 65 years of age) with DSM-IV ADHD.[148] Subjects started with 18 mg of OROS methylphenidate HCl once daily. After 8 days, the dose was increased and maintained on 36 mg for the following 20 days. If necessary and depending on the therapeutic response, the dosage could be increased to 54 mg on Day 28 to a maximum dose of 72 mg on Day 56 to reach the optimum dose for each patient. Fifty-eight subjects were evaluable for efficacy. Significant improvements were found in the Brazilian version of Adult ADHD Quality of Life (AAQoL) Scale, both on total as well as on each subscale. Similarly, ADHD symptom improved with the Adult Self-Rating Scale (ASRS) scores significantly reduced from baseline at Weeks, 4, 8, and 12. A significant reduction in scores of CGI-I, Hamilton's Depression Rating Scale, and State and Trait Anxiety Inventory were also observed. This study provides the first evidence of QoL improvement in a Brazilian clinical sample of adults with ADHD treated with OROS methylphenidate HCl. None of these patients were exposed during the reporting period.

Non-Company Sponsored Trials

Pediatrics/Adolescents

Brain activation with functional magnetic resonance imaging (fMRI) was evaluated during a reward sensitivity paradigm, which consisted of high monetary reward (HMR) and low monetary reward (LMR) conditions before and after 3-month treatment with OROS methylphenidate HCl in 17 children and adolescents (10 to 16 years of age) with ADHD and 17 age- and sex-matched healthy controls in Kumamoto University Hospital in Japan.[149] The ADHD subjects were administered 18 to 36 mg OROS methylphenidate HCl per day for 3 months. Decreased activation of the nucleus accumbens and thalamus was observed in ADHD subjects before treatment during the LMR condition only, which improved after treatment to the same level as those of the healthy controls. The observed change in brain activity was associated with improved ADHD symptom score, which were derived from the Japanese versions of the ADHD-RS-IV.

A retrospective, single-centre, observational review of paediatric ADHD subjects (5 to 18 years of age) who met DSM-IV criteria who were prescribed and adequately controlled on

[148] Mattos P, Louza MR, Palmini ALF, de Oliveira IR, Rocha FL. A multicenter, open-label study to evaluate the quality of life in adults with ADHD treated with long-acting methylphenidate (OROS MPH): Concerta Quality of Life (CONQoL) Trial. *J Atten Disord*. 2013; 17(5): 444-448.

[149] Mizuno K, Yoneda T, Komi M, Hirai T, Watanabe Y, Tomoda A.. Osmotic release oral system – methylphenidate improves neural activity during low reward processing in children and adolescents with attention-deficit/hyperactivity disorder. *Neuro Image: Clin* 2. 2013; 366-376.

OROS methylphenidate HCl for at least 1 month was conducted and included 153 subjects.[150] Of the 153 subjects, 53 were switched to novo-methylphenidate extended-release capsule (Novo-methylphenidate ER-C) and 100 remained on OROS methylphenidate HCl. The primary outcome was the proportion of subjects who destabilized. Destabilization was defined clinically as a change in symptoms and/or function resulting from a change in ADHD medication and dosage. Eighty seven percent of subjects destabilized with a switch from OROS methylphenidate HCl to Novo-MPH-ER-C, whereas only 26% of subjects who remained on OROS methylphenidate HCl experienced destabilization. Of the 87% of subjects who destabilized when switched to Novo-methylphenidate ER-C, 43% reported a shorter duration of action and 78% eventually restabilised on OROS methylphenidate HCl. Of the 26% of subjects who destabilized despite remaining on OROS methylphenidate HCl, 54% required an increase in dosage and 46% required a change in medication.

Adults

In a randomized, double-blind, placebo- and active-controlled, parallel-group, multicentre trial, Weisler et al. (2012) evaluated 3 dosages of bavisant (a histamine H3 receptor antagonist) and two active controls in 430 adults (18 to 55 years of age) with DSM-IV diagnosed ADHD.[151]. Four hundred and twenty-four subjects were randomized to 1 of 6 treatment groups and received at least 1 dose of study drug as follows: placebo; bavisant 1 mg/day, 3 mg/day, 10 mg/day; atomoxetine hydrochloride 80 mg/day; or OROS methylphenidate HCl 54 mg/day (n=68) to be taken for 42 days. Doses were titrated in atomoxetine (40 mg/day for the first 3 days and 80 mg/day for the remainder of the trial) and OROS methylphenidate HCl (36 mg/day for the first 3 days and 54 mg/day for the remainder of the trial). A total of 335 completed the trial. Of the 68 subjects in the OROS methylphenidate HCl arm, 55 subjects completed the trial. Six of these losses were due to adverse events, 2 were lost to follow-up and 5 due to other reasons. There were no therapeutic failures in the OROS methylphenidate HCl arm. Mean change from baseline in the total ADHD Rating Scale-Version IV (ADHD-RS-IV) score at day 42 was not statistically superior to placebo in the bavisant 10 mg/day group. However, mean change from baseline in the total ADHD-RS-IV score at Day 42 in atomoxetine and OROS methylphenidate HCl were statistically superior to placebo. Secondary efficacy assessments demonstrated a similar pattern with a non-significant trend towards improvement in the bavisant groups. The authors noted a robust separation of OROS methylphenidate HCl from placebo.

17.3. Characterisation of Benefits

The 4 studies that became available during the reporting period of 11 October 2012 to 31 October 2013 included the following:

[150] Van Stralen JPM. The clinical impact of switching attention deficit hyperactivity disorder subjects from OROS-MPH to Novo-MPH ER-C®: a paediatric practice review. *Paediatr Child Health*. 2013. 18(2): 70-73.

[151] Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassman-Mayer C. Randomized clinical study of a histamine H3 receptor antagonist for the treatment of adults with attention-deficit hyperactivity disorder. CNS Drugs. 2012; 26(5): 421-434. LMD309847.

- Two trials in children/adolescents: 1 randomized, controlled trial examining the effect changes in brain reward circuitry during treatment, and 1 retrospective review comparing treatment efficacy in subjects who either continued OROS methylphenidate HCl treatment throughout the trial or switched from OROS methylphenidate HCl to Novo-MPH-ER-C.
- Two studies in adults: 1 multicentre, open-label trial assessing the effect of treatment on QoL scores; and 1 double-blind, placebo-controlled, and active-controlled trial.

These new studies do not alter the benefit profile of OROS methylphenidate HCl. Important baseline efficacy and effectiveness information is presented in Section 17.1 and Section 18.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

There have been no significant changes to the benefit or risk profile of OROS methylphenidate HCl during the reporting period. The overall appraisal of the benefit risk for OROS methylphenidate HCl remains favourable for the approved indications and populations. The benefits of these treatments outweigh the risks, which can be mitigated principally through product labelling.

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

Medical Need

Methylphenidate is a mild central nervous system stimulant thought to block the reuptake of norepinephrine and dopamine into presynaptic neurons and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a recommended first-line pharmacotherapy for the management of ADHD and has been used to manage symptoms of this disorder for over 50 years. The efficacy of methylphenidate in the management of the core symptoms of ADHD has been well established. However, immediate-release methylphenidate has a duration of effect of only 3 to 4 hours, which has led to the development of extended-release formulations. Pharmacodynamic studies demonstrated that in order to achieve duration of effect with methylphenidate of up to 12 hours, a controlled release generating an ascending plasma concentration profile for methylphenidate would be required. This has been achieved using OROS technology, and allowed the development of OROS methylphenidate HCl (a prolonged-release formulation with duration of effect of 12 hours).

OROS methylphenidate HCl is indicated as part of a comprehensive treatment program for ADHD in children (over 6 years of age) and adults when remedial measures alone are insufficient.

Epidemiology

ADHD is a developmental condition of inattention and distractibility, with or without accompanying hyperactivity. According to the DSM-5, adults or children must have an onset of symptoms before the age of 12 years that cause significant social or academic impairment. Many individuals are diagnosed after the symptoms have been present for a number of years, especially in the case of those with Predominantly Inattentive Type.

The essential feature of ADHD, as described in DSM-5 is a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and more severe than is typically observed in individuals at a comparable level of development. Some impairment from the symptoms must be present in at least 2 settings (eg, at home and at school or work). There must be clear evidence of interference with developmentally appropriate social, academic, or occupational functioning. The disturbance does not occur exclusively during the course of Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and is not better accounted for by another mental disorder (eg, Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder).

ADHD is typically chronic in nature with an unclear onset; therefore, prevalence provides a better estimate of the burden of ADHD. ADHD is one of the most common neurobehavioral disorders of childhood and can persist through adolescence and into adulthood.

The reported prevalence rates vary depending on the nature of the population sampled and the method of ascertainment. ADHD prevalence rates from 2.2% to 8.9%, and the majority of all studies in general indicate prevalence rates ranging from 4% to 10%.[152] In a large meta regression analysis, Polanczyk et al. (2007) found ADHD/HD worldwide-pooled prevalence to be 5.29% (95% Confidence Interval=5.01–5.56); the large variability of ADHD/HD prevalence rates worldwide resulted mainly from methodological differences across studies.[153]

No clear correlation with mortality exists in ADHD. However, studies suggest that in childhood, ADHD is a risk factor for subsequent conduct and substance abuse problems which may increase risk of mortality.[154]

The pathology of ADHD is not clear, and the health risk is primarily psychosocial. However, exact morbidity had not been quantified. A person with ADHD may struggle with impairments in crucial areas of life, including relationships with peers and family members, and performance at school or work. Some studies have demonstrated increases in substance abuse, risk-taking, and criminal behaviours among adolescents and adults who have ADHD.[155] Increases in unintentional injuries and health care utilization have been noted in some studies of people with ADHD. [156,157]

[152] Skounti M, Philalithis A, Galanakis E. Variations in prevalence of attention deficit hyperactivity disorder worldwide. *Eur J Pediatri*. 2007; 166: 117-123.

[153] Polancyzk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. 2007; 164: 942-948.

[154] Barkley RA, Murphy KR, Kwasnik D. Motor vehicle driving competencies and risks in teens and young adults with attention deficit hyperactivity disorder. *Pediatrics*. 1996; 98: 1089-1095.

[155] Cuffe SP, Moore CG, McKeown RE. Prevalence and correlates of ADHD symptoms in the national health interview survey. *J Atten Disord* 2005; 9: 392-401.

[156] Wilens TE. The nature of the relationship between attention-deficit/hyperactivity disorder and substance use. J of *Clin Psychiatry*. 2007; 68(Suppl 11): 4.

[157] DiScala C, Lescohier I, Barthel M, Li G. Injuries to children with attention deficit hyperactivity disorder. *Pediatrics*. 1998; 102: 1415-1421.

It is difficult to establish a diagnosis of ADHD in children younger than age 4 or 5 years, because their characteristic behaviour is much more variable than that of older children and may include features that are similar to symptoms of ADHD. After childhood, symptoms may persist into adolescence and adulthood, or they may ameliorate or disappear. The percentages in each group are not well established, but as many as 65% of children with ADHD will have the disorder or some residual symptoms as adults. In a trial using data from the National Comorbidity Survey Replication (NCS-R), adult persistence of ADHD, defined as the conditional prevalence of clinician-assessed ADHD in adults among the 8.1% of NCS-R respondents classified as having had ADHD in childhood, was estimated to be 36.3% in the total sample. Persistence does not differ significantly between respondent sex, age, or race-ethnicity.[158]

Therapeutic Alternatives

Four classes of pharmacotherapy have shown efficacy in ADHD:

Stimulants

These are first-line treatment in all published guidelines.[159,160]

Methylphenidate

Immediate-release forms of methylphenidate are approved for treatment of ADHD. Onset of action is within 30 to 60 minutes. The duration of effect is 3 to 6 hours requiring dosing 3 times daily at the initiation of treatment. This allows for flexibility in titration of dose at the initiation of therapy but can make assessment problematic as there is a rebound after the effect of the drug has waned, which may lead to an erroneous assumption of treatment failure by parent-observers. After a few weeks of treatment, dosing intervals can often be increased. A common side effect is insomnia, which is most noticeable if a dose is taken late in the afternoon. Extended-release forms are available.

Dexmethylphenidate

This is the d-enantiomer of methylphenidate. At equivalent dosage the efficacy is similar to methylphenidate as is the adverse drug reaction profile.

[158] Kessler RC, Adler LA, Barkley R, et al. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. *Biol Psychiatry*. 2005; 57: 1442-1451.

[159] Seixas M, Weiss M, Müller U. Systematic review of national and international guidelines on attention-deficit hyperactivity disorder. *J Psychopharmacol* 2012; 26: 753-765.

[160] Banaschewski T, Coghill D, Santosh P, et al. Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. *Eur Child Adolesc Psychiatry* 2006; 15: 476-495. LMD236491.

Dextroamphetamine

Dextroamphetamine is the d-isomer of d,l-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Amphetamines promote release of dopamine and norepinephrine into the synapse and inhibit their reuptake into the presynaptic cell. It has similar efficacy to methylphenidate, but results in more adverse effects.[161] Dextroamphetamine also has a short half-life necessitating multiple daily doses. An extended-release preparation is also available.

Lisdexamphertamine

Lisdexamphetamine is an inactive drug. After ingestion, it is converted to l-lysine, and active d-amphetamine, which is responsible for its activity. The conversion to d-amphetamine is not affected by gastrointestinal pH and is unlikely to be affected by alterations in normal gastrointestinal transit times.[162] It has a duration of effect that allows for once daily dosing. In a Phase 3 trial, lisdexamphetamine was shown to be superior to placebo.[163] Its side effect profile was similar to dextroamphetamine.

Amphetamine Mixed Salts

Despite its long availability, there are few substantial randomized controlled trials for amphetamine mixed salts. A meta-analysis of 4 studies compared it to methylphenidate. Although there was a trend in favour of the amphetamine, statistical significance was achieved in only 1 outcome. [164]

Non-stimulants

This class has the advantage of avoiding drug abuse, which is a significant social problem for all of the stimulant drugs. There is 1 approved member in this class.

Atomexetine

Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter, with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Gibson et al (2006)[165] reviewed 5 trials comparing atomoxetine to stimulants. No significant

[161] Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics* 1997; 100: E6.

[162] Shojaei A, Ermer JC, Krishnan S. Lisdexamfetamine dimesylate as a treatment for ADHD: dosage formulation and pH effects. Poster presented at: Annual Meeting of the American Psychiatric Association; May 19-24, 2007; San Diego, CA.

[163] Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther*. 2007; 29: 450-463.

[164] Farone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficity/hyperactivity disorder: a meta-analysis. *J Clin Psychopharmacol*. 2002; 22: 468-473.

[165] Gibson AP, Bettinger TL, Patel NC, Crismon ML. Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother*. 2006; 40: 1134-1142.

differences between atomoxetine and methylphenidate immediate-release were found on the ADHD Rating Scale total score. OROS methylphenidate HCl showed significantly greater improvement at Weeks 1 and 2, and significantly more subjects treated with OROS methylphenidate HCl were classified as responders.

Antidepressants

Although bupropion and imipramine have been widely used, they have not been approved for use in ADHD.

Alpha-2 adrenergic Agonists

Both clonidine and guanfacine have been approved for use in the USA. Guanfacine is approved for single agent and adjuvant use. The main drawbacks to treatment are sedation and fatigue with hypotension and bradycardia seen less frequently. Clonidine has a similar profile but has rather less data from randomized controlled trials.

18.2. Benefit-Risk Analysis Evaluation

Integrated benefit-risk assessment methodology:

The integrated benefit-risk assessment is based on a systematic framework that is composed of: (1) defining the context of use; (2) identifying the key benefit and risk attributes that drive the benefit-risk balance; (3) summarising the data associated with the key benefit and risk attributes; and (4) interpreting the benefit-risk profile in the context of the data and its strengths, limitations, and uncertainties. This approach integrates clinical and scientific data with expert clinical judgment, allowing for a systematic and transparent evaluation of the overall benefit-risk profile of OROS methylphenidate HCl for the treatment of ADHD in children and adolescents aged 6 to 17 and adults aged 18 to 65 who meet DSM-IV criteria for ADHD.

Context of use:

OROS methylphenidate HCl is currently authorized for the treatment of ADHD in children, adolescents, and adults. The nature of untreated and currently treated ADHD, and the benefits and limitations of existing alternative treatments, are described in Section 18.1 above.

Key benefits:

OROS methylphenidate HCl is unique compared to other ADHD medications, as it offers 12-hour control of symptoms. The product's innovative technology helps distinguish itself from other extended-release psychostimulants by delivering methylphenidate in a continuously ascending profile throughout the day, without increased risk for side effects, food effects, or concern over operating machinery or vehicles. The once-daily dosing of OROS methylphenidate HCl can improve adherence and decrease the potential for mid-day wear-off effects or rebound because the controlled drug release results in lasting clinical efficacy through 12 hours.

Overall assessment of benefit:

Children/Adolescents

In all studies and across all assessments, patients receiving OROS methylphenidate HCl had significantly better attention and over activity scores than patients receiving placebo. There were no statistically significant differences between OROS methylphenidate HCl and methylphenidate 3 times daily treatments. Improvement was consistent across setting (home, school), raters (parents, community, and laboratory schoolteachers and investigators), and instruments (IOWA Conners, SKAMP, and SNAP-IV), which also showed appropriate response in first-time users of methylphenidate started on OROS methylphenidate HCl. These effects were also comparable with the effects of methylphenidate 3 times daily treatments. The efficacy of OROS methylphenidate HCl was sustained for 12 hours post-dosing and for the duration of the treatment (short and long treatments). The analysis of numbers and proportion of discontinuations for lack of efficacy or for any reason revealed that approximately 11% of patients receiving OROS methylphenidate HCl or methylphenidate 3 times daily discontinued for lack of efficacy, compared to 43% receiving placebo.

Evidence for the long-term maintenance of effect in children/adolescents comes from 2 long-term studies demonstrating that OROS methylphenidate HCl effectiveness was maintained for up to 2 years.

Adults

The efficacy of OROS methylphenidate HCl was demonstrated in 3 DB, placebo-controlled Phase 3 trials in subjects between 18 and 65 years of age who demonstrated a chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before the age of 7 years. Based on the change from baseline in the primary efficacy variable, OROS methylphenidate HCl was significantly superior to placebo when administered as a fixed dose of 18, 36, or 72 mg/day (Trial 3002) and at an individualized dose of 36 to 108 mg/day (Trial 02-159). Trial 3013 was specifically designed to evaluate the incremental benefit/risk profile of the proposed maximum dose for adults (72 mg/day) relative to the maximum dose currently approved in the EU for children and adolescents (54 mg/day). The trial was not designed to demonstrate the superiority of 72 mg/day over 54 mg/day. Based on the change from baseline in the primary efficacy variable, the 72 mg dose was significantly superior to placebo, whereas the 54 mg dose was not. OROS methylphenidate HCl improved both the severity of

ADHD symptoms and subject functioning in all 3 trials. The onset of therapeutic effect was early, beginning with the first assessment (Week 1 in Trial 3002) and the first assessment of the assigned dose (Week 3 in Trial 3013).

Evidence for the long-term maintenance of effect comes from several sources. The randomized withdrawal phase of Trial 3004 was intended to provide primary support for the maintenance of effect. Although the trial failed to demonstrate a statistically significant difference between subjects assigned to continued OROS methylphenidate HCl treatment and those assigned to placebo for the primary efficacy variable, OROS methylphenidate HCl differentiated from placebo on a secondary outcome measure (CGI-I). Secondary support for the maintenance of effect comes from Trial 3013, which showed that the statistical superiority of the 72 mg dose over placebo was maintained throughout the 13-week double-blind period. In each published trial, improvement of ADHD symptoms was maintained for the 6-month duration of the trial. Finally, in long-term, open-label studies lasting for 6 or 12 months (Trial 12-304) or up to 2 years (Trial 3004 OL), subjects receiving doses of 18 to 108 mg/day experienced improvement in ADHD symptoms. Although these were open-label studies, the relevance of their results for the demonstration of maintenance of effect comes from the fact that at least 50% of the subjects who entered these studies completed long-term treatment and the percentages of subjects who withdrew due to lack of efficacy were low, suggesting that these subjects were continuing to experience clinically relevant benefits from OROS methylphenidate HCl treatment.

New Efficacy Data

During the period covered by this report, 4 publications (2 in children, 2 in adults) provided positive efficacy data on the use of OROS methylphenidate HCl in the treatment of ADHD; these trials are summarized in Section 17.1. Efficacy with OROS methylphenidate HCl was similar to that at approval, supporting a continued favourable benefit profile.

Strengths, limitations, and uncertainties of the evidence of benefit:

The benefits of OROS methylphenidate HCl in the treatment of ADHD in children, adolescents, and adults are supported by prospective, randomized, active-comparator controlled trials, which support the basis of approval for the authorized indications. These trials are summarized in Section 17.1.

Key Risks:

Cardiac Disorders

As part of the EU Article 31 referral conditions, the MAHs were requested to evaluate data from a study co-ordinated by the US FDA, AHRQ, and the Vanderbilt University. The first part of the final study report was published in November 2011 in the New England Journal of Medicine and the results found no increased risk for serious cardiovascular events (ie, sudden cardiac death, acute myocardial infarction, and stroke) in the 1,200,438 children and young adults (2-24 years old) receiving an ADHD drug (adjusted hazard ratio, 0.75; 95% confidence interval [CI], 0.31 to

1.85)[166]. The second part of the study was published in December 2011 in the Journal of the American Medical Association[167] and described the effect of ADHD medication and cardiovascular events in young and middle-aged adults (25-64 years old). The authors similarly concluded that use of ADHD medication was not associated with an increased risk of serious cardiovascular events.

The Company reviewed both final study reports in conjunction with other methylphenidate MAHs and submitted an evaluation of the study reports to the MHRA on 26 April 2012. The evaluation concluded the Multi-Centre, Observational Cohort Study to Assess the Cardiovascular Risks of Medications Prescribed for Attention Deficit Hyperactivity Disorder (ADHD) is considered to represent the best available evidence concerning the risk of serious cardiovascular (CV) events in both paediatric and adult patients exposed to ADHD medications including MPH. The conclusion was reached given the scope of the studies (with cohorts including 1,200,438 children and young adults, covering 2,579,104 patient years follow-up including 373,667 person-years of current use of ADHD medicines, with MPH accounting for 51% of current use), as well as, the comprehensiveness of the study design. The published findings did not demonstrate an increased CV risk to be associated with the use of MPH, or the overall group of ADHD medications evaluated, in the paediatric population. The findings were also noted to be supported by the results of 2 other recent epidemiological studies[168,169] on CV risk with stimulants in a paediatric population. In addition, results from the same FDA/AHRQ/Vanderbilt study in the middle-aged adult population are similar to those in the paediatric population.

The MHRA in its RMP FAR of the core RMP received on 24 September 2012 confirmed that no further regulatory action was recommended with regards to this safety concern and that the RMP was sufficient.

According to Warnings and Precaution Section of the current CCDS for OROS methylphenidate HCl[170], *"Although a causal relationship has not been established, sudden death has been reported in patients with structural cardiac abnormalities treated with ADHD drugs with stimulant effects. These treatments should be used with caution in patients with structural cardiac abnormalities"* and *"caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. [Blood pressure (especially for patients with hypertension) and heart rate should be monitored at appropriate intervals in patients taking (OROS methylphenidate HCl)]."* The following statement is included in the Interactions section of the current OROS methylphenidate HCl CCDS, *"Because of*

[166] Cooper WO et al. ADHD drugs and serious cardiovascular events in children and young adults. *NEJM* 2011 first published online 01 November 2011. doi:10.1056/*NEJMo*a1110212.

[167] Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA* 2011;306(24):2673-83.

[168] Olfson M, Huang C, Gerhard T et al. Stimulants and cardiovascular events in youth with Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry* 2012;51(2):147-156.

[169] Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. *Pediatrics* 2011;127:1102-10.

[170] Janssen Research & Development, L.L.C. Company Core Data Sheet, CONCERTA Dated 15 May 2012.

possible increases in blood pressure, [OROS methylphenidate HCl] should be used cautiously with vasopressor agents." [OROS methylphenidate HCl] is *"contraindicated in patients on monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor"* due to a risk of hypertensive crisis.

The following are listed adverse events in the OROS methylphenidate HCl CCDS: Angina pectoris, Blood pressure increased, Bradycardia, Cardiac murmur, Chest discomfort, Chest pain, Extrasystoles, Heart rate increased, Hypertension, Palpitations, Raynaud's phenomenon, Supraventricular tachycardia, Tachycardia, and Ventricular extrasystoles.

In the current PBRER/PSUR, the following MedDRA SMQs were selected to identify cases for review: Myocardial Infarction SMQ (Narrow), and Other Ischaemic Heart Disease SMQ (Narrow).

Results

The search described above identified 9 cases[171] (8 initial, 1 follow-up) reported during the current reporting period which were analysed. Review of the cases did not identify new safety information with respect to cardiac disorders.

Suicidality

There is evidence of a direct association between ADHD and suicide, with overlapping symptoms such as impulsiveness, disruptive behaviour, irritability, and problems with the law.[172,173,174] A published literature review[175] determined that the rate of completed suicide in boys/men (aged 5 to 24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population. A separate study using a US managed care database determined that patients with an ADHD diagnosis (adults and children) were nearly 3 times more likely to make a suicide attempt (Odds Ratio=2.9 95% CI: 2.4, 3.5) than age and gender-matched controls.[176]

Suicide is identified in the OROS methylphenidate HCl RMP[177] as an event of important potential risk and depression is an important identified risk in patients taking methylphenidate products. The Company submitted a final meta-analysis report on the risk of suicidality with a

[redacted]

[172] James A, et al. *Acta Psychiatr Scand*. 2004:110:408-415.

[173] Jacobs, Harvard Medical School Guide to Suicide Assessment and Intervention. 1999.

[174] Rappley M. *N Engl J Med*. 2005;352:165-173.

[175] James A, et al. *Acta Psychiatr Scand*. 2004:110:408-415.

[176] Swensen AR (2002), Allen AJ, Kreusi M, et al. Increased risk of self-injury and suicide risk for patients with attention deficit/hyperactivity disorder. *Eur Neuropsychopharmacol* 2002;12:S421.

[177] Janssen Research & Development, L.L.C. CONCERTA RMP, Version 3.0; 19 December 2009. EDMS-PSDB-10643608:3.0

previous PSUR dated 09 Dec 2011.[178] The results demonstrated that methylphenidate does not seem to increase the risk of suicide or self-harm-related events relative to placebo in children and adolescents with ADHD. Enhanced pharmacovigilance by the company of the potential risk of suicidality continues through the use of a targeted questionnaire.

Suicide is unlisted in the OROS methylphenidate HCl CCDS; however, depression is listed as an ADR in the Adverse Reactions Section of the CCDS.

The following MedDRA SMQs were selected to identify cases for review that were reported during the current reporting period: Depression and suicide/self-injury SMQ (contains Depression [excluding suicide and self-injury] and Suicide/self-injury SMQ).

There were 5 cases of completed suicide, 1 suicidal behaviour, 9 suicidal ideation, 20 suicide attempt, 1 case of suicidal depression and 1 case each of intentional self-injury, self-injurious behaviour and self-injurious behaviour. There were 17 cases of depressed mood, 43 cases of depression and 3 cases of major depression reported during the current period.

ADHD patients are subject to inherent background risks for suicidal behaviour. In the US, the annual rate of completed suicide for those aged 10 to 19 years is 4.6 per 100,000 persons.[179] A 2004 literature article entitled, Attention deficit hyperactivity disorder and suicide: A review of possible associations determined that the rate of completed suicide in males (aged 5 to 24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population.[180] An article entitled Screening for suicide risk in adults: A summary of the evidence for the U.S. Preventative Services Task Force described risk factors seen in patients who have completed suicide and more than 90% of those who complete suicide have a diagnosable psychiatric illness at the time of death, usually depression, alcohol or substance abuse, or both.[181]

Adverse events reported during the current period that were consistent with suicidality (one case can contain multiple adverse events) include: Completed suicide (2); Intentional overdose (5); Intentional self-injury (1); Self-injurious behaviour (3); Suicidal behaviour (1); Suicidal ideation (9) and Suicide attempt (20). Adverse events consistent with depression/depressed mood reported during the current period include: 19 cases of Depression and 1 case of Major depression. All cases were reviewed in the recent OROS methylphenidate HCl PSUR and no new safety issues with respect to suicide, self-injury or depression were identified.

[178] Janssen Research & Development, L.L.C. CONCERTA PSUR Dated 22 November 2011. EDMS-ERI-28940479:1.0

[179] Miniño AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: Final data for 2000. National Vital Statistics Reports, 50(15). Hyattsville, MD: National Center for Health Statistics, 2002.

[180] James A, Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: A review of possible associations. *Acta Psychiatr Scand*. 2004(110): 408-415.

[181] Gaynes BN, West SL, Ford CA, Fram P, Klien J, Lohr KN. Screening for suicide risk in adults: A summary of the evidence for the U.S. Preventative Services Task Force. *Ann Internal Med*. 2004;140(10):822—837.

Additional Identified and Potential Risks:

Important identified risks for methylphenidate products listed in the OROS methylphenidate HCL EU-RMP dated 17 December 2009 and subject to ongoing routine pharmacovigilance practices by the Company include: Hypertension, Tachycardia, Raynaud's phenomenon, Hallucinations (auditory, skin sensation, visual disturbance), Psychosis/Mania, Anorexia, Aggression, Depression, Decreased rate of growth.

Routine pharmacovigilance practices are also ongoing for the following important potential risks also listed in the current EU-RMP: Migraine, Repetitive behaviours, QT prolongation, Cyanosis, Arrhythmias, Ischaemic cardiac events, Sudden death, Cerebrovascular disorders, Hostility, Tics/Tourette's syndrome/Dystonias, Carcinogenicity, Effect on final height, Sexual maturation (delayed), Off-label use, Diversion, Withdrawal syndrome, Drug abuse and Drug dependence, Lymphocytic leukaemia, Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea) and Neonatal effects on growth.

Cases reporting identified and potential risks were reviewed in the current PBRER/PSUR and no changes to the CCDS were warranted.

Overall assessment of risk:

Strengths, limitations, and uncertainties of the evidence of risk:

The post-marketing experience for OROS methylphenidate HCl is extensive, as this product was first approved in 2000. No new risks were identified during the reporting period that alters the benefit-risk profile. OROS methylphenidate HCl continues to have a favourable benefit-risk profile for ADHD in children and adults.

Integrated benefit-risk evaluation conclusions:

OROS methylphenidate HCl is an effective treatment for ADHD. The benefit is maintained over the [1-year] period studied. The impact on patients' lives is in both clinical measurements (efficacy endpoints) and quality of life assessments (QOL instrument). The important potential risks tend to occur with similar frequency in patients with ADHD.

The post-marketing safety data of OROS methylphenidate HCl remains favourable. There are no new safety data available during this period that have meaningfully altered the overall benefit risk profile for the approved indication. The benefit-risk balance remains positive.

19. CONCLUSIONS AND ACTIONS

During the period of this update, no new efficacy information with OROS methylphenidate HCl has been identified. Consequently, there has been no change to the efficacy section of the prescribing information or patient information.

After the period of this update, the following previously unrecognised ADRs with OROS methylphenidate hydrochloride were identified:

- Priapism
- Increased Libido

Evaluation of these ADRs is ongoing.

OROS methylphenidate HCl continues to have a favourable benefit-risk profile for the treatment of patients with ADHD. The Company will continue to monitor suspect adverse reactions in association with the use of OROS methylphenidate HCl.

Continuous Company safety monitoring will ensure that updated safety information is available.