EMA/PRAC/355408/2017
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Active substance(s): methylphenidate

Procedure No.: PSUSA/00002024/201610

Data lock point: 31.10.2016

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	10 February 2017	10 February 2017
☐	Lead Member State preliminary assessment report (AR)	11 April 2017	13 April 2017
☐	MS/PRAC members and MAH comments	11 May 2017	16 May 2017
☐	Lead Member State updated assessment report following comments	29 May 2017	31 May 2017
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	9 June 2017	9 June 2017

Rapporteur assessment comment: [redacted] Therefore no further action is proposed [redacted]

Self-injurious behaviour

Shire – undertook a review to focus exclusively on self-injurious behaviour exclusive of suicide. From this, 12 cases were identified, of these 7 were serious but none were fatal. Serious cases included events such as self-mutilation, banging head on floor, self-strangulation and self-harm (cutting arm). Of the 7 serious cases, 2 had insufficient information to assess causality and 1 was assessed as unlikely related to Equasym (and associated names). The remaining 4 serious cases were assessed as possibly related to Equasym (and associated names) due to the temporal relationship, and 3 of the cases recovered upon discontinuation of Equasym (and associated names). The MAH also notes that the background prevalence is greater in patients with ADHD.

Novartis –.

In order to identify relevant cases, the noteworthy case definition used is: a well-documented HCP case presenting with events of intentional self-injury, self-injurious behavior or self-injurious ideation; with a plausible time to onset, positive de-challenge/re-challenge information, and without a more plausible alternative explanation such as underlying medical history, concurrent conditions or concomitant medications known to cause such behavior.
Cumulatively, 54 cases have been reported and can be stratified by formulation as follows:

Table 15-4 Formulation wise distribution for cases of Ritalin for "Self-injurious behaviour"

Formulation	No. of cases (%)
Ritalin Immediate-release tablet	17 (31.48%)
Ritalin Sustained-release tablet	0
Ritalin Modified-release capsule	8 (14.81%)
Unknown	29 (53.70%)
Total	**54**

Of the 17 IR cases, 6 were poorly documented, and 7 had additional risk factors. One resulted in suicide. In two cases causation could be ruled out, however in the remaining 2, causation could not be ruled out due to Ritalin IR.

Of the 8 MR capsules cases, cases were excluded either due to limited information, background history, or causal role unlikely.

Of the 29 unknown formulations, 14 cases were poorly documented with limited information for assessment. Nine cases had additional risk factors like underlying medical conditions, concomitant medications and lack of drug effect. Of these 14, in one case the patient died, however information whether patient committed suicide or it was homicide by step father was unknown. He was hospitalised with physical injuries and diagnosed with self-injury, seizure and overdose of Ritalin. After discharge the patient was found dead at home. This patient, of school age had previously told his teacher of physical abuse by his step father, therefore the cause of death was unclear.

In four cases, the patient developed self-injurious behavior while being off Ritalin, hence causal role of Ritalin was unlikely. In the remaining two cases, the causal role of Ritalin could not be ruled out; however these two cases did not fulfil the noteworthy case definition criteria.

Of the total 54 case reports, 33 were in patients <18years. Of these, causation could not be ruled out in 2 cases. Twelve cases were in patients >18 years, although causation could not be attributed to Ritalin. Similarly in the 9 cases in patients of unknown age, causation could not be attributed to Ritalin. The MAH notes that self-injury is more common in children with spectrum autism than those with other neurodevelopmental disabilities. Similarly, although self - injury is not usually a suicide attempt, it can increase the risk of suicide because of the emotional problems that trigger self-injury. And the pattern of damaging the body in times of distress can make suicide more likely.

Medice- Cumulatively, Medice has only received 2 case reports related to the group of self-injurious behaviour since marketing authorisation. First case was about self-harm and received in 2013. It concerned a ~ 11 year old male patient of unknown ethnicity. No medical history or concomitant medications were provided. The patient received MPH with unknown dose, dates and indication. On an unspecified date, the patient had a suicide attempt and self-harm. The outcome of the events has not been reported. No further data was provided or could be collected. It could not be identified if the child was taking IR or prolonged-release medication. The other case was about compulsive skin picking. It concerned an 8 year-old male patient who experienced psychosis (scratching inter alia) during treatment with IR Medikinet tablets for an unknown indication. The event occurred after increase of Medikinet dosage from 25 mg to 30 mg. The event resolved after reduction to 20 mg.

Janssen – a review was undertaken to examine cases of suicide/self-injury up to 31 October 2014, and as a supplementary update between 01 November 2014 and 31 October 2016. During the supplementary period, 85 cases have been identified. These are summarised in the following table.

Table 55: Distribution of MedDRA PTs, Source, and Region for Cases in MedDRA SMQ Suicide/Self Injury (narrow) Reported With Methylphenidate HCl

MedDRA PT	Number of Cases[a]
Suicidal ideation	38
Suicide attempt	23
Intentional overdose	19
Intentional self-injury	9
Completed suicide	8
Suicidal behaviour	3
Self-injurious ideation	2
Depression suicidal	1
Source	
Spontaneous	67
Literature	14
Solicited	4
Region of Origin	
North America	33
European Union	24
Rest of World	15
Japan	13
Total Cases	**85**

Key: MedDRA= Medical Dictionary for Regulatory Activities; PT= Preferred Term; SMQ= Standardised MedDRA Query

a: A single case may report more than 1 MedDRA PT of interest.

The majority of cases concerned males, and children ≤17 years of age. Of the 38 cases reported in children ≤17 years of age, 78.9% were males. Note; ages were unknown is 17 case reports. In terms of self-injury, causation could not be identified as attributable to OROS-MPH, however may have been associated with suicidal ideation/suicide. One such case was identified in a 16-year-old female treated with OROS® methylphenidate HCl initiated on an unspecified date for ADHD. An unspecified duration later after initiating treatment, the patient rooted out her hair, started talking nonsense, and attempted suicide. She was hospitalised on the same day. An unspecified duration later, treatment with OROS® methylphenidate HCl was withdrawn and the patient was discharged. The patient recovered from the event of suicide attempt. Causation could not be assessed owing to the lack of information. Temporal relationship cannot be determined owing to the lack of information concerning initiation or withdrawal of treatment.

In the following two cases, causation could not be ruled out however the background medical history may have contributed to the event of suicidal ideation.

One case of suicide involved a 14-year-old male with medical history of spina bifida occulta was treated with OROS® methylphenidate HCl (27 mg) for ADHD. Previously, the patient had a drug history of lisdexamfetamine dimesylate for the same indication for approximately 1 month prior to switching to OROS® methylphenidate HCl. Concomitant medications were not reported. Approximately 2 weeks after initiating treatment with OROS® methylphenidate HCl, the patient developed suicidal ideation and depression. Treatment with OROS® methylphenidate HCl was withdrawn and treatment with sertraline for depression was initiated. The patient recovered from the event of suicidal ideation.

A 26-year-old female who was treated with OROS® methylphenidate HCl for ADHD and reported the MedDRA PT of Suicidal ideation. Concomitant medications reported were drospirenone/ethinyl estradiol. Four hours after administration of OROS® methylphenidate HCl, the patient developed listlessness, anxiety, depressed mood, and suicidal ideation. Twenty days later, the treatment with OROS® methylphenidate HCl was withdrawn. The patient had recovered from listlessness, anxiety, depressed mood, and suicidal ideation,

A trending analysis was undertaken based on the number of case reports and exposure rate.

Table 61: Worldwide Reporting Rates for Spontaneous Cases Reporting Suicidality Related-Events Identified With OROS® Methylphenidate Hydrochloride per Interval (11 October 2011 Through 31 October 2016)

Interval	Reporting Period	Post-Marketing Exposure (Person-Years)	Number of Cases	Reporting Rate (per 100,000 Person-Years)
1	11 October 2011 to 10 October 2012	[redacted]	45	[redacted]
2	11 October 2012 to 31 October 2013		34	
3	01 November 2013 to 31 October 2014		42	
4	01 November 2014 to 31 October 2015		38	
5	01 November 2015 to 31 October 2016		36	

Key: PBRER= Periodic Benefit Risk Evaluation Report; PSUR=Periodic Safety Update Report

a: Exposure taken from PBRER/PSUR covering 11 October 2011 to 10 October 2012 (01 October 2011 to 30 September 2012).

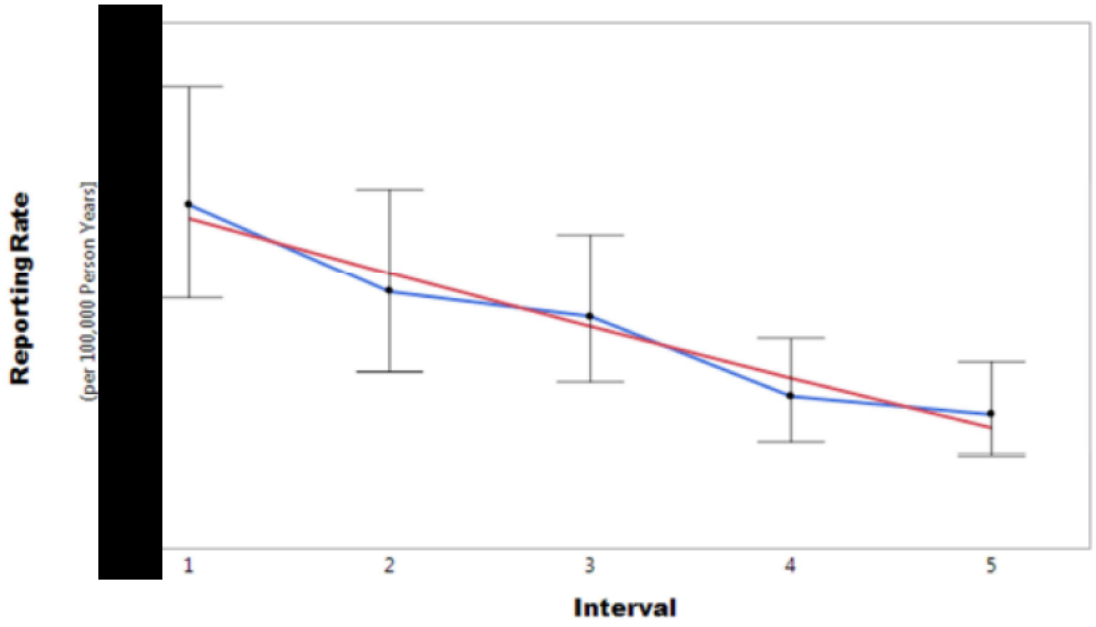
b: Exposure taken from PBRER/PSUR covering 11 October 2012 to 31 October 2013 (01October 2012 to 31 October 2013).

c: Exposure taken from PBRER/PSUR covering 01 November 2013 to 31 October 2014 (01 October 2013 to 30 September 2014).

d: Exposure taken from PBRER/PSUR covering 01 November 2014 to 31 October 2015 (01 November 2014 to 31 October 2015).

The following figure shows the RRs and reporting trend for suicidality-related events per 100,000 person-years exposure to OROS® methylphenidate HCl from 11 October 2011 through 31 October 2016.

Figure 19: Worldwide Reporting Rates for Spontaneous Cases Reporting Suicidality-Related Events Identified With OROS® Methylphenidate Hydrochloride per Interval (11 October 2011 Through 31 October 2016)



From this, it can be seen that the reporting rate is decreasing owing to the increased exposure to OROS-MPH but no apparent increase in case reports.

Rapporteur assessment comment: only one MAH specifically looked for cases of self-injurious behaviour exclusive of suicide/suicidal ideation. It is difficult to separate the two but are not extricabley bound. An example is given concerning the 8 year old who was identified with compulsive skin picking after receiving an increased in dose of Medikinet. This condition resolved following a reduction in dose.

The trend analysis undertaken by Janssen-cilag shows a reduction in reporting rate, however does not take into account that reporting itself may be under-represented owing to an increased familiarity of the drug. Post-marketing exposure has increased although the number of reports received by the MAH has remained at the same level, therefore it is not surprising that the reporting rate decreases.

Care needs to be taken when each application is reviewed according to noteworthy definitions. Many cases lack that specific information and cannot reach all the relevant criteria.

Reporting of self-injury may be misrepresented or unrecognised, as in the case of the female who was reported to be rooting out her hair, possibly regarded as a symptom of mania although the eventual outcome was suicide attempt. The patient was discharged as recovered from the attempt, although the outcome in relation to the underlying condition is unknown. Mania, anxiety, and suicidal ideation/suicide are all stated in the SmPCs as warnings and examples of psychoses. Self-harm and self-injury is also associated with depression. Again depression is a known risk and is highlighted in the SmPCs for all MPH products. Similarly, patients who have a medical history of psychoses are contraindicated in the treatment with stimulants in section 4.3 of the SmPC mirrored in the PL in terms that are understood by the patient or carer as follows:

• Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.

• Diagnosis or history of severe and episodic (Type 1) Bipolar (affective) disorder (that is not well controlled)

The SmPCs and patient leaflets contain warnings concerning depression, suicidal ideation/suicide in section 4.4 and 4.8; however these do not specifically address the risk of self-injurious behaviour.

Based on the data reviewed there is insufficient evidence to support further regulatory action at this time. However, non-suicidal self-injurous behaviours should remain under close monitoring.

Data provided by [redacted]

The [redacted] identified 463 children and adolescents (10-19) between 2011 and 2015, from the Swedish Poisons Information Centre in the category “suicide attempts or overdoses in some other self-destructive purpose” (from methylphenidate).

The data from the Swedish Poison Information centre also highlighted cases involving alternative medicines used in the treatment of ADHD[5], although the journalist notes that the highest number of cases involve the use of MPH;

[5] GIC2011to20125

Antalet överdoseringsfall där Giftinformationscentralen blivit kontaktad och som av GIC:s personal registrerats som självdestruktiv handling angående ungdomar 10-19 år

	2011	2012	2013	2014	2015	Totalt
Atomoxetin	19	11	22	10	16	78
Licenspreparat, amfetamin	0	1	1	1	0	3
Lisdexamfetamin	0	0	0	11	24	35
Metylfenidat	96	86	98	102	81	463
Totalt	115	98	121	124	121	579

Antalet tillbud med angivna läkemedel där Giftinformationscentralen blivit kontaktad angående barn 00-04 år

	2011	2012	2013	2014	2015	Total
Atomoxetin	11	6	14	5	7	43
Licenspreparat, amfetamin	1	2	5	1	2	11
Lisdexamfetamin	0	0	0	2	16	18
Metylfenidat	41	46	46	44	59	236
Total	53	54	65	52	84	308

The [redacted] has obtained information concerning the doses used, gender and age in some of these cases[6]. Unfortunately individual case information has not been provided and therefore full assessment of this information is not possible at this time, however some brief listing has identified doses reported in some cases:

Gender	Number	Age range (years)	Age unknown
Male	41	13 - 19	3
Female	82	12 - 19	2
Total	123		

	Ritalin	Concerta	Equasym	Medikinet	MPH

[6] ChildrenSelfHarm ADHD2014

Min dose	80	108	330	160	288
Max dose	1920	2700	360	1200	288

The doses used are not reported in all cases; hence the maximum dosage taken may be greater than described in the above table, for example a description of the patient taking the whole bottle.

Rapporteur assessment comment:

The number of case reports of suicidal behaviour reported to the Swedish Poison Centre for methylphenidate between the ages 10 – 19 years has remained relatively constant. Although the numbers do not appear to be improving, exposure has increased greatly over the period in question, therefore the relative proportion in terms of overall exposure, is decreasing. The number of cases reported to the poison centre for children 00-04 years between 2011 - 2015 is more variable, peaking in 2015. The reason for this is unknown.

It cannot be assessed from this data as to the reasons for the overdoses described. The range of doses consumed is wide for some products, and less so for others. The maximum doses described may be as a result of intentional overdose (either as a single agent or in a mixed cocktail); the lower doses could equally be as a result of accidental or unintentional overdose. Unfortunately this data does not inform us of the prescribed indication for treatment (on- or off-label), or the intention of the patient (suicidal ideation, self-injury, abuse, medication error). The outcome of each case, time to onset, or possible causation, is not known.

The risk of suicidal behaviour is greater in patients with ADHD. Suicide and suicidal ideation is an identified risk for all ADHD medicines and has been highlighted in product information and educational materials. Self-injury that is not associated with suicidal ideation has not been brought out from this data; therefore it is not possible to make any further assessment of self-injury exclusive of suicide/suicidal ideation from this data.

2.4. Characterisation of risks

Cardiovascular disorders

Shire

The were no case reports of QT-prolongation or valvulopathy or sudden death, cyanosis, neonatal cardiorespiratory toxicity, or epistaxis during this reporting period. The following tables summarise the numbers of cardiovascular disorders reports of concern;

Table 2: Tachycardia-related events (pediatric vs. adult population) – number of cases

Preferred Term	Pediatric (<18 years)	Adult (≥18 years)	Unspecified age
Tachycardia	1	0	1