EMA/PRAC/373592/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Active substance(s): methylphenidate

Procedure No.: PSUSA/00002024/201710

Data lock point: 31/10/2017

Status of this report and steps taken for the assessment[1]			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	15 February 2018	15 February 2018
☐	Lead Member State preliminary assessment report (AR)	16 April 2018	17 April 2018
☐	MS/PRAC members and MAH comments	16 May 2018	16 May 2018
☐	Lead Member State updated assessment report following comments	31 May 2018	31 May 2018
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	14 June 2018	14 June 2018

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date

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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for methylphenidate.

For an overview of the nationally authorised products for which PSURs were submitted in the context of this EU single assessment, please see the appendix to this assessment report.

2. Assessment conclusions and actions

This is the third Periodic Safety Single Assessment Report (PSUSA) for methylphenidate (MPH), which presents information for the reporting period 1 November 2016 to 31 October 2017.

Methylphenidate is a well-established medicinal product available in a number of different formulations, covering a wide release profile. The formulations can generally be split into 3 groups; instant release (IR), modified release (MR) and sustained release (SR). Dexmethylphenidate is the dextrorotary form of methylphenidate.

MPH is indicated in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children between the ages of 6 and 18 years and adults. Most products presented have an indication of treatment of ADHD in the children and adolescents between 6 and 18 years, however a number also include an adult indication or continuation of treatment into adulthood. With the development of the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM), more adults are being identified who have not been diagnosed before. In reflection of this, products containing MPHe have recently been authorised for the initiation of treatment in adults with ADHD not previously diagnosed. As a consequence, MPH is increasingly being prescribed throughout the European Union within both the paediatric and the adult population.

The largest proportion of spontaneous reports relate to psychiatric and central nervous system (CNS) disorders which are known to be predominant in this patient population. No new safety signals were identified from these case reports.

A large number of literature articles have been identified concerning non-clinical and clinical studies, case reports and overviews. Most articles refer to the approved indication, the remaining are exploratory of the use of MPH in alternative indications which are not authorised. Some of the papers refer to mechanism of action, genetic influence on ADHD, or patterns and experiences of abuse. All provide some insight into the growing background knowledge concerning ADHD and pharmacological treatments, benefits and risks. The PRAC considered each literature reference within the context of the reviewed safety concerns. Although a number of articles reporting safety signals have been identified, these publications are in line with the known safety profile of MPH and do not alter the benefit-risk profile of the product.

A number of new signals have been raised during the reporting interval, including MPH & gynecomastia/increased prolactin (remains open for next reporting period to identify additional cases); Raynaud Phenomenon (closed, labelling changes undertaken) and OROS MPH and Photophobia (closed, without labelling changes).

Signals closed during this interval include toxicity to various agents (subject to review of additional case summaries from MAH), logorrhoea and priapism (product information updated).

Significant ongoing signals include self-injurious behaviour, drug-induced liver injury, off-label use, misuse and abuse; interaction between long-acting formulations and antacids, H2 blockers / proton pump inhibitors, lack of efficacy with switching.

One MAH (Janssen) raised a signal in the interval for cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion) concluding these events are considered possibly associated with the use of OROS MPH. Consequently, the risk of cerebrovascular disorders has been addressed in Section 4.8 of the SmPC.

Based on the data reviewed regarding self-injurious behaviour the PRAC considers that there is insufficient evidence to support further regulatory action at this time. However, the signal remains ongoing and should remain under close monitoring in future PSURs. Current labelling and risk minimisation measures are deemed appropriate. Despite the number of cases regarding drug-induced liver injury and evidence for causality remains weak and no regulatory action is proposed at this time, the signal remains under close monitoring at the request of PRAC.

In the PRAC Recommendation for the previous PSUSA (June 2016), the PRAC requested the MAHs of the longer-acting formulations to present information on the release profiles of their formulations in terms of relative gastric acidity and to ensure that the correct advice is provided in the product leaflet (PL). The MAHs were also requested to consider whether a change in the release profile could have an effect on efficacy. Based on the review of the available data, no information was identified to support a definitive causal association between long acting formulations and antacids and H2 blockers / proton pump inhibitors. No updates to product information are warranted.

Off-label use, misuse and abuse remain an ongoing safety concern associated with MPH. This is a well-described public health concern. The off-label use occurs for increased academic performance. Increased concentration and attention and includes the use by university and higher vocational education students. The reporting rate (RR) for off-label use for Ritalin is significantly higher for this reporting interval as is the RR for Janssen OROS-MPH. The increase in off-label use raises concern given the decreased exposure noted in this reporting interval. The large number of cases reported for off-label use with the indication ADHD may relate to the growing use of MPH in the adult population.

There are uncertainties associated with all the listed safety concerns, and therefore all important safety concerns will remain for continued pharmacovigilance monitoring.

Cases of suicidality have been reported in both adults and children. However, there is not enough evidence to suggest a clear causal link with MPH given the increased incidence associated with the underlying condition of ADHD.

Due to increasing use of MPH in adults, there is a safety concern regarding MPH use during pregnancy. The safety concern pertaining to exposure in pregnancy differs between RMPs of each MAH, however all MAHs seem to capture cases of exposure in pregnancy in their PSURs at some degree. In order to further investigate this safety concern, the MAHs are asked to provide a cumulative review of cases of ‘exposure in pregnancy’ in the next PSUR.

The safety concern on cardiomyopathy in children was reviewed in 2009 as part of a referral procedure in accordance with the Article 31 of Directive 2001/83/EC. The CHMP concluded that cardiomyopathy was not considered to be an important safety concern for children and adults due to the rarity of the event in this age group, however there are uncertainties in other age groups. Cardiomyopathy was added to the RMP of the originator, Ritalin, as a potential risk, following authorisation of some Ritalin products for use in adults. In the context of the above mentioned referral procedure, the CHMP also recommended that further studies should be carried out on the long-term effects of MPH (ADDUCE

study). Following the previous PSUSA, the PRAC requested that a more comprehensive cumulative review of cardiomyopathy, including left ventricular hypertrophy and myocardial infarction to be presented in this PSUSA. Overall this obligation has not been adequately met by all MAHs. The assessment of the available publications on the ADDUCE study has not been undertaken by all MAHs and adequate consideration has not been given to the impact of the available data on existing product labelling and RMMs. Therefore, the MAHs are requested to provide a more considered review of all relevant published data from the ADDUCE project and discuss its relevance to the current characterisation of risks for cardiomyopathy, myocardial infarction and left ventricular hypertrophy once this becomes available. The PRAC outlined that the reviews should include a detailed literature search including review of all emerging publications from the ADDUCE study and should not be confined to case reports of MAHs own branded products.

Having reviewed all available data regarding cardiomyopathy and MPH treatment, including the supplementary information submitted by MAHs and the comments from the member states, it is concluded that there is insufficient evidence to support MPH as a cause of cardiomyopathy for the time being. The conclusion is consistent with the current labelling and the routine risk minimisation measures which are already in place.

However, due to the risk of increase in blood pressure and the biological plausibility for cardiomyopathy, the potential risk of cardiomyopathy and related terms cannot be fully excluded. PRAC considers that this safety risk (cardiomyopathy) should be present as an important potential risk in the RMP for all EU products in line with the RMP of Ritalin. An additional risk minimization measure (aRMM) is already in place to educate physicians on the use of MPH in accordance with the safety guidance given in the safety sections of the core EU MPH SmPC. The PRAC considered a number of updates may be necessary, including the consideration of drafting separate educational materials for children, adolescents and adults, as some safety concerns addressed by the educational materials (for example those pertaining to growth) may not be applicable for both groups. Therefore, the MAHs of the innovator product is requested to assess the suitability of the educational material in relation to the adult population.

Overall, there has been no change in the related safety concerns of left ventricular hypertrophy and myocardial infarction and no additional risk within this SMQ could be identified.

No additional risk minimisation measures are proposed for any of these safety concerns at this time.

3. Recommendations

Based on the review of data on safety and efficacy by the Lead Member State and taking into account any comments provided by the PRAC, the PRAC considers that the risk-benefit balance of medicinal products containing the active substance Methylphenidate remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. Issues to be addressed in the next PSUR:

In addition, the MAH(s) should also address the following issues in the next PSUR:

1. The MAHs should continue to report cumulative exposure data stratified by EU Member state and world-wide.

2. In order to monitor the evolving prescribing patterns in the adult population the MAHs should present adult and paediatric exposure separately. This is not only applicable for those products with an adult indication but for all products, as most report some degree off label use or continuation of therapy into adulthood.

3. MAHs should continue to monitor

   - Intentional self-injury and self-injurious ideation
   - Drug induced liver injury
   - Rhabdomyolysis
   - Gynecomastia/increased prolactin

4. All MAHs are asked to provide a cumulative review of cases of 'exposure in pregnancy' in the next PSUR.

5. All MAHs are requested to provide a review of any published data from the ADDUCE Consortium and discuss its relevance to the current characterisation of risks, risk minimisation measures and product labelling for Cardiomyopathy, Myocardial Infarction and Left Ventricular Hypertrophy, once this information becomes available.

5. PSUR frequency

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

6. Other considerations

In addition, MAH(s) which have an RMP in place should update the RMP to include 'Cardiomyopathy' as an important potential risk (in line with the RMP of the innovator product), in the next RMP update to be submitted within an upcoming regulatory procedure affecting the RMP or at the latest by 1st December 2018.

The MAH of the innovator product should review the educational materials and discuss if these additional risk minimisation measures (aRMMs) adequately address the risks associated with the indication of ADHD in adults. Should this critical analysis necessitate the update of the aRMMs, a work-sharing (WS) variation should be submitted within three months. In the absence of the need of such variation, the MAH shall submit the results of this critical analysis in the next PSUR.

Ongoing Signals &

New information on other potential risks not categorised as important

Self-injurious behaviour

Source/Trigger- PRAC PSUR Assessment Report Procedure No. PSUSA/00002024/201610.

Novartis/Sandoz

A search was conducted in the Novartis Global Safety Database (Argus) using the MedDRA (version 20.0) in order to retrieve relevant cases. The search terms included: PTs "Intentional self-injury" and "Self-injurious ideation". The focus of analysis in this section is to assess the causal association of reported AEs of self injurious behaviour to Ritalin/ Focalin treatment.

No relevant information suggesting a causal association of self-injurious behaviour with Ritalin and Focalin therapy has been identified from clinical trials and literature.

Three cases of Ritalin and one case of Focalin were retrieved during the reporting period.

	Age Range	**Release Profile**	**No of cases**	**Case Details**
Ritalin	< 18 Years	Immediate-Release Tablet	1	, concurrent autism. Became aggressive and wanted to hurt herself. Insufficient information for adequate medical assessment.
Ritalin	18 to 60 years	Unknown Formulation	1	, polymedicated with concurrent PTSD, haemangiomas in CNS, spinal cord and brain. Was depressed, suicidal thoughts, panic attacks and anxiety. Underlying conditions were risk factors for events.
Ritalin	Unknown	Immediate-Release Tablet	1	, following self-discontinuation of Ritalin developed idea of self-injury. Time to onset and triggering factors unknown.
Focalin	<18 Years	Unknown Formulation	1	patient with depression and anxiety. Concomitant guanfacine hydrochloride, fluoxetine hydrochloride and clonazepam. Developed abnormal behaviour with suicidality and self-injurious behaviour. Concurrent conditions

				and concomitant fluoxetine are risk factors.

The cumulative data includes a total of 57 Ritalin 10 Focalin cases. The review of the cases from this reporting interval is consistent with the findings from the review of cumulative data. During the reporting interval, none of the cases retrieved for Ritalin and Focalin reported with a fatal or life-threatening outcome for the event of interest. Evidence for causality was identified to be weak. The RR of current reporting interval is lower than previous reporting intervals and cumulative period. Due to the similarity in the general bioequivalence/ pharmacokinetic (PK) among the different Ritalin formulation, no significant differences are expected in the AE profile between the different Ritalin formulations. The background incidence of self-injurious behaviour in general population was not available.

Mylan

A search of the safety database, using MedDRA PT intentional self-injury, Self injurious Ideation identified no cases were reported during the interval period. Cumulatively one case was identified with event mapping the above terms. No literature article, clinical trial data, non-interventional study data received during interval period. As per current RSI and updated SmPC (Methylphenidate Hydrochloride 5 mg Tablets, Generics UK T/A Mylan, dated –05-Apr-2017) non-suicidal self-injurious behaviours is unlisted. MAH proposes to continue close monitoring.

Lead Member State assessment comment:
A review of the risk of self-injurious behaviour was undertaken in the last PSUR (01 Nov 2015 to 31 Oct 2016). Many of the cases were excluded due to lack of information or were associated with other risk factors for self-harm. Self-harm may be associated with the diagnosis of alternative psychoses including suicidality and depression, although that not all patients who self-injure have the intention to commit suicide. The SmPCs and patient leaflets have warnings concerning suicidality and depression, however these do not specifically address self-injurious behaviours. Based on the data reviewed at the time there was insufficient evidence to support further regulatory action at this time. The cases presented here are either confounded by concomitant medication or underlying condition, or lack information for adequate causal assessment. However, self-injurious behaviours should remain under close monitoring in future PSURs.

Drug-induced liver injury

Source/Trigger- PRAC PSUR assessment (PSUSA/00002024/201510, dated 09 Jun 2016), a cumulative analysis of DILI was performed in PSUR 01 Nov 2015 to 31 Oct 2016.

Novartis/Sandoz:

Based on the review of the available data in the previous PSUR (01 Nov 2015 to 31 Oct 2016), no information was identified to support a definitive causal association between Ritalin/Focalin and DILI. Evidence for causality was identified to be weak and no change to the current CDSs was recommended in the last PSUR.
DILI is not listed in the current CDSs and not considered as identified or potential risk in the RMP.

Five cases of Ritalin (3 serious, 2 non-serious) and no Focalin cases during the reporting interval. In most of the cases there was limited information for causality assessment. Two cases were in the age range < 18, two cases 18-60 years and one case >60. No case fulfilled the criteria of Hy's law and no noteworthy case was identified. One serious case was of note: