EMA/PRAC/355408/2017
EMA/PRAC/355408/2017
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

The literature report (Munk et al 2015) was not described in the PSURs. This case identified an 11 year old boy who was treated with a maximal dose of MPH (54 mg per day) for ADHD and Tourettes. The duration of exposure to MPH is unknown, however the report refers to cardiac arrest and/or arrhythmias, occurring within approximately 3 instances during exercise. The author referred to the large cohort study (Cooper et al 2011). The authors Munk et al describes the cohort study as not being able to identify a single case of myocardial infarction, however this is incorrect as 9 cases (0.3/100,000 person-years) of myocardial infarction were reported in this study. Cooper et al (2011) concluded that methylphenidate did not increase the relative risk of serious cardiovascular events although the upper bound of the 95% CI could not rule out this risk. Munk et al conceeds that, "*myocardial infarction and sudden cardiac death are extremely rare among children during treatment with methylphenidate. However, the present case shows that myocardial infarction can happen due to methylphenidate exposure in a cardiac healthy child, without any other cardiovascular risk factor".* Therefore the two publications are in agreement.

Overall, the MAHs concluded that there was no change in the safety concern of ischeamic cardiovascular event and no additional risk within this SMQ could be identified. These conclusions are endorsed.

Additional risk minisation measures are in place to monitor cardiovascular parameters at the initiation of treatment and on a regular basis during treatment with MPH. On the basis of these reviews, no further regulatory action is justified.

[Confidential information deleted] comment:

1. The data based on the cases from the Swedish Poison Information Center should be taken into consideration with caution as those cases are not reported adverse events but rather a summary based on the telephone contacts to this center. The Swedish Poisons information Centre answers questions about acute poisonings, and gives advice about suitable treatment in cases of poisoning received from the general public or healthcare professionals. The data concerning the cases are based on the descriptions during the calls and are not verified with healthcare records. Please find the following description of data provided by the Swedish Poison Information Center:

Concerning the child's "intake dose or amount":
The pharmacist at service always tries to obtain information around dose or amount taken, as this is critical to the assessment of risk. The information given can vary from being very exact and precise, perhaps directly from the patient (correct or not) to pure guesses from people around the patient in question. For this very reason we would never ourselves use this data for analyses or publication, as it is considered of too low quality.

Concerning "if the consequence of the overdose was hospitalization/hospital care":
We always register, in a searchable way, what our treatment recommendation is. The alternatives when the inquirer is the general public are *"no/simple action"* or *"seek hospital advice/care"*. When talking to a health care provider (e.g. ambulance or hospital staff) the alternatives are *"treatment recommendation: hospital care"* or *"seek hospital advice/case"*. As mentioned above the tables describing this data are enclosed.
Please note that we generally do not have the information around what actually did happen after the conversation, i.e. whether the consequence indeed was e.g. hospitalization or not.

Concerning "did the child take his /her personal medication or someone else's":
As is obvious from our print-out this information is almost never included, as it is not asked for. The reason is that it is unimportant for assessing risk, or for concluding the correct treatment recommendation in the acute situation.

Concerning "context around the overdose (e.g. connection with alcohol or other drugs)":
As is obvious from our print-out this information is not consistently documented. It is important to understand that lack of such information in a case does not necessarily mean that e.g. alcohol or other drugs were not present.

Based on all above, it would not be possible to leave individual case information related to this data.

2. A subgroup of children (0-4 years) is also included in this assessment. Poisoning cases in 0-4 year olds are in general due to the nature of the children's curiosity and can hardly be due to suicide attempt or self-destructive purpose. This aspect should be reflected within the assessment.

Rapporteur assessment comment:

It is useful to hear the description of the information gathered in the Swedish Poison centre. It is agreed that this data will not provide the necessary information for analysis as the relevant information is not provided to the centre.

Comments regarding Cardiomyopathy

[Confidential information deleted] comments;

As a reminder, the risk of cardiomyopathy was reviewed as part of the article 31 referral. It was considered that it was not an important safety concern owing to the rarity of the event in children. Following the variation to include an adult indication for Ritalin LA, cardiomyopathy was added to the Ritalin RMP as a potential risk. In the PSUR covering the period 1 November 2013 - 31 October 2014, a cumulative analysis identified case reports in patients below and above the age of 18 years. This data supports the inclusion of cardiomyopathy as an important potential risk although it cannot be determined whether this relates to all MPH products, or to specific age groups. An updated cumulative review was requested in the current PSUR covering the 2015-2016 period.

Following the updated cumulative review of cardiomyopathy cases requested as part of the previous PSUSA, the LMS concludes that it is apparent that the event of cardiomyopathy is due to long-term use in patients 17 years and over. Hence, the LMS endorses the inclusion of the ADR "cardiomyopathy" in the SmPC for methylphenidate products with adult indications. However, this SmPC update is not requested in the PSUSA recommendations. Based on the cumulative review data, the SmPC section 4.8 update of this products with the risk of "cardiomyopathy" should be requested as part of this PSUSA. Also, this risk should be considered as an important identified risk in adult in the next PSUSA and RMP for products with an indication in adult.

To be noted that, in the previous PSUSA procedure, [Confidential information deleted] highlights the case of a 41 year-old woman treated with methylphenidate for 2 years when she presented dyspnoea and restrictive cardiomyopathy. No cardiovascular medical history was reported. She was treated with dexfenfluramine during few months 20 years before dyspnoea beginning. Treatment with methylphenidate started in 2009. She presented dyspnoea in 2011 at rest and effort. Cardiac catheterization shows a post-capillary pulmonary hypertension at effort. Clinicians concluded on a diagnosis of restrictive cardiomyopathy with dyspnoea and hyperventilation syndrome possibly related to methylphenidate. Methylphenidate treatment is stopped in 2011. In 2016, the patient presented clinical and hemodynamic improvement.