<Doc ref.>
Pharmacovigilance Risk Assessment Committee (PRAC)

Lead Member State PSUR updated preliminary assessment report

Active substance(s): methylphenidate

Procedure No.: PSUSA/00002024/201510

Data lock point: 31 October 2015

Lead Member State:	UK
Lead Member State contact person:	< contact person name and email>
Lead Member State assessor	[redacted]
EMA Procedure Manager:	[redacted]

Status of this report[1] and steps taken for the assessment				
	Procedure start date:			11 February 2016
☐	Member State preliminary Assessment report (AR)	22 April 2016	Comments by:	22 May
	Comments from the MAH(s) received on:			<Date>
☒	Assessment report updated following comments:			26 May 2016
	An Oral explanation took place on:			<Date>
☐	Final PRAC assessment report adopted with recommendation adopted on:			09 June 2016

Updated text is shown in blue throughout the document

[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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

© European Medicines Agency, 2016. Reproduction is authorised provided the source is acknowledged.

Table of contents

Table of contents **3**

List of abbreviations **4**

2. Preliminary assessment conclusions and actions **5**

3. Preliminary Recommendations **6**

4. PSUR frequency **8**

Annex: Preliminary PRAC/ Lead Member State assessment comments on PSUR **9**

1. PSUR Data **10**

1.1. Introduction 10
1.2. Worldwide marketing authorisation status 10
1.3. Overview of exposure and safety data 10
1.3.1. Actions taken in the reporting interval for safety reasons 10
1.3.2. Changes to reference safety information 17
1.3.3. Estimated exposure and use patterns 18
1.3.4. Data in summary tabulations 23
1.3.5. Findings from clinical trials and other sources 26
1.3.6. Lack of efficacy in controlled clinical trials 36
1.3.7. Late-breaking information 36

2. Signal and risk evaluation **38**

2.1. Summary of safety concerns 38
2.2. Signal evaluation 39
2.3. Evaluation of risks and new information 42
2.4. Characterisation of risks 51

3. Benefit evaluation **54**

4. Benefit-risk balance **56**

5. Lead Member State Request for supplementary information **57**

6. MAH(s) responses to preliminary recommendations for issues to be addressed in the next PSUR **58**

List of abbreviations

ADHD – Attention Deficit / Hyperactivity Disorder

AE – Adverse Event

ADRs – Adverse Drug Reactions

ADRQ – Agency for Healthcare Research and Quality

CNS – Central Nervous System

CT – Clinical Trials

DLP – Data Lock Point

DSM IV – Diagnostic manual and Statistical manual of Mental disorders, fourth edition

DSM 5 - Diagnostic manual and Statistical manual of Mental disorders, fifth edition (2013)

DUS – Drug Utilisation Study

EC – European Commission

EU – European Union

Formaterat: Svenska (Sverige)

EU-RMP – EU Risk Management Plan

FDA – Food and Drug Administration (US)

HCP – Healthcare Professional

ICHRs – spontaneous Individual Case Safety Reports

IMP – investigational product

MA – Market Authorisation

MAH – Market Authorisation Holder

MPH - Methylphenidate

OROS - Osmotic controlled-Release Oral delivery System

PSUR – Periodic Safety Update Report

RMP – Risk Management Plan

RR – Reporting Rate

PMS – Post Marketing Surveillance

PSP – Patient Support Programs

PT – Preferred Term

SmPC - Summary Product characteristics

US – United States

USPI – US package insert

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.

In addition to the period covered in the EURD list, the report includes and lists PSURs submitted for previous periods in the context of a PSUR worksharing.

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. Preliminary assessment conclusions and actions

This is the first Periodic Safety Update Single Assessment (PSUSA) for methylphenidate (MPH), which presents information for the reporting period covering 01 November 2012 to 31 October 2015. The European Union Reference Date (EURD) is 06 October 1954.

MPH indicated in Europe as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to the current DSM criteria or ICD guidelines and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

Novartis, Shire and Medice also hold MAs for MPH authorised for treatment of ADHD newly diagnosed in adults. In summary for these products diagnosis is to be made according to DSM criteria, structured interview and based on a very thorough assessment of the severity and chronicity of the symptoms and their impact on the daily life of the patient. Diagnosis cannot be made solely on the presence of one or more symptom. Overall exposure to MPH either as a longer-acting formulation or an instant release formulation, is increasing and percentage prescribing to adults is also increasing.

As expected the largest proportion of spontaneous reports originate from the SOCs psychiatric disorders and nervous system disorders which are known to predominate in this patient population. Of interest, are the cumulative reports of self-injurious behaviour; intentional self-injury; Dermatillomania; and self-injurious ideation, of which a higher proportion are reported for the 'longer acting' formulation Osmotic controlled-Release Oral delivery System- Methylphenidate (OROS-MPH). Whilst the overall numbers of self-injurious reports may be considered low, self-injury can have serious consequences. Therefore all the market authorisation holders (MAHs) of MPH products are requested to keep the adverse reactions (ADRs) relating to self- injurious behaviour under close scrutiny and provide an updated review in the next PSUR.

The recognised safety concerns for MPH remain unchanged. Both Ritalin and OROS-MPH have very similar safety profiles, although Ritalin includes the additional safety concern of cardiomyopathy which has not been added to the OROS-MPH table of safety concerns. Conversely OROS-MPH includes the identified risk of priapism.

Cardiomyopathy was reviewed in the article 31 referral and it was considered that it was not an important safety concern owing to the rarity of the event in children. Cardiomyopathy was added to the Ritalin RMP as a potential risk following the variation to include an adult indication for Ritalin LA. 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. Therefore all the market authorisation holders (MAHs) of methylphenidate products are requested to keep the safety concern of cardiomyopathy under close scrutiny and provide an updated review in the next PSUR.

The signal of Priapism was highlighted in previous PSUR assessments and has been under review through successive PSURs. Priapism is an important safety concern for OROS-MPH, but is not identified as an important safety concern in the RMPs for alternative MPH MAs. Priapism is a painful and debilitating event, with potential serious sequalae. Albeit in low numbers, serious case reports of Priapism continue to be identified although case report information is limited. Therefore an updated cumulative review should be undertaken by all MAHs, and to consider if the event is related to age, time to onset, withdrawal, and/or formulation.

The signal of Rhabdomyolysis was added to the US product insert in April 2015 but within the submitted PSURs little to no information has been provided to either support or refute it. In the PSUR for Equasym / Medadate / Quasym, the MAH Shire presented a cumulative review of reports identifying rhabdomyolysis, however only identified 1 case report that was confounded by concomitant therapy bupropion. Given that only one case was identified in a cumulative review undertaken by Shire and few spontaneous reports identified by Janssen Cilag and Novartis; in terms of considerable patient exposure it is sufficient to keep this under close review at this time. However, a cumulative review should be undertaken for further assessment in the next PSUR.

Janssen Cilag has identified a new signal of Drug Induced Liver Injury (DILI) with prolonged use of OROS-MPH. This has not been identified for the Ritalin products, although a high number of spontaneous reports of hepatobiliary disorders are reported. Consequentially further characterisation of these spontaneous reports should be provided and a review of all cases of DILI provided in the next PSUR by all MAHs.

Medice has identified an increased reporting of the interaction of their long-acting formulation with proton-pump inhibitors. This has not been reported by the other MAHs. It is theoretically possible that a change in the gastric acidity may have an effect on the release of the active product. All MAHs should review reports of interaction between their long-acting formulations and antacids, H2-receptor blockers/ proton pump inhibitors to further examine this possibility.

Whilst the recognised safety concerns have not altered for all MPH medicines; new safety concerns have been identified by the MAHs that differ between OROS-MPH and Ritalin. OROS-MPH is a 'longer acting' formulation; therefore reports presented in the PSURs for this product are specific to this 'longer acting' formulation. PSURs for MPH cover both instant release and 'longer acting' formulations, therefore in order to determine if these new signals are related to formulation, presentations of reported and suspected ADRs according to formulation will aid future evaluation. Overall, based on the information received during the review period, it is concluded that the benefit-risk balance of MPH in the licensed indication for the treatment of ADHD remains unchanged.

3. Preliminary 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 <by consensus/majority decision> 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).

Conditions to the Marketing Authorisation(s) for nationally authorised products:

The marketing authorisation holder(s) for MPH shall complete the below conditions;

Provisions of educational materials continue to be made available to healthcare professionals and patient/carers.

Issues to be addressed in the next PSUR:

In addition, the MAH(s) should also address the following issues in the next PSUR (DLP 31 October 2016):

1. All MAHs are recommended to undertake a cumulative review of all cases of self-injurious behaviour.
2. All MAHs should submit a cumulative review of case reports of cardiomyopathy.
3. The ADR of DILI should be closely monitored for all MPH medicines in successive PSURs as an ongoing signal and a cumulative review provided in the next PSUR. Taking into account the 2 serious cases of hepatic disorders leading to a liver transplantation assessed in variation II77 for Concerta, the MAHs should further analyse cases leading to liver transplantation as part of the cumulative review. MAHs should consider whether there is a need for an update of section 4.4 of the SmPC.
4. The MAHs should provide a cumulative review of Rhabdomyolysis with the provision of more detailed information on the individual case reports and conclusion.
5. All MAHs are recommended to undertake a cumulative review of all cases of priapism and associated terms within HLT Erection and ejaculation conditions and disorders using MedDRA v19 in the next PSUR. MAHs should ensure that all sources of data are researched, and the maximum amount of information including age, time to onset, the underlying conditions, concomitant medications, instant release or 'longer-acting' formulation, if the event occurred in the treatment period or in the period the patient did not take MPH (e.g. drug holidays, drug discontinuation), the dosage and the reported positive de- and re-challenges. It is essential that those MAHs who hold MAs for both the 'longer-acting' and the instant release formulations provide additional information on the formulation specified in the case reports.
6. The MAHs of the longer-acting formulations are required to present information on the release profiles of their formulations in terms of relative gastric acidity to ensure that the correct advice is provided in the SmPCs and Patient information. MAHs should consider whether a change in the release profile could have an effect on efficacy. All MAHs should undertake a cumulative review of reports concerning interactions with antacids, H_2 receptor blockers/ proton-pump inhibitors.
7. All reports of lack of efficacy as a result of a switch between MPH products should be discussed in more detail. All potential underlying causes should be taken into consideration, including time to onset, manufacturer, formulation, or drug-drug interaction.
8. In future PSURs, analysis of safety in terms of MPH formulation should be presented separately in those PSURs where multiple formulations are included.
9. The MAHs are requested to discuss the recent publications (Storebø OJ *et al* 2015, and Eugenia Chan *et al* 2016) in the next PSUR (DLP 31 October 2016) in terms of benefit.

In addition, MAH(s) which have an RMP in place should address the issues, as detailed in section 2 of the Assessment report, in the next RMP update to be submitted within an upcoming regulatory

procedure affecting the RMP or at the latest within 90 days of adoption of the final AR (by 9 September 2016)

4. 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.

Annex: Preliminary PRAC/ Lead Member State assessment comments on PSUR

1. PSUR Data

1.1. Introduction

Methylphenidate (MPH) is a central nervous system stimulant drug which was developed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) (Psychostimulants - ATC code: NO6B AO4) and outside the EU for narcolepsy. The CNS stimulant effect is thought to be due to inhibition of dopamine reuptake in the striatum, without triggering dopamine release.

It is available as an immediate release product and various forms of 'longer acting' formulations including an osmotic controlled-release oral delivery system (OROS) methylphenidate. The pharmaceutical forms available include tablets, capsules, and oral solutions.

Immediate release, modified or extended release products are available with strengths 5mg, 10 mg, 20 mg, 30 mg, 40 mg, 50mg and 60 mg providing for a maximum daily dose of 60mg in children and adolescents <18 years and 80mg in adults. Prolonged release products are available with strengths 18 mg, 27 mg, 36 mg, and 54 mg, providing for a maximum daily dose of 54mg.

Within this PSUSA, all MPH products will be assessed and discussed together, with the exception of OROS-methylphenidate (OROS-MPH) which will be assessed and discussed separately. All pharmaceutical formulations of Ritalin will be referred simply as 'Ritalin' unless data is specifically derived from one specific formulation.

1.2. Worldwide marketing authorisation status

MPH was first authorised in 6 October 1954 in Switzerland and OROS-MPH first authorised in 01 August 2000 in the US (see appendix for authorisations in Europe).

Lead Member State/PRAC assessment comment: MPH is a well-established medicinal product. In the EU, its use is primarily for the treatment of children and adolescents, although may be continued into adulthood if the patient is considered clinically stable. However, following the revision of the diagnostic manual DSM IV to DSM 5, it has been recognised that ADHD may be apparent in Adults who have not previously be identified, therefore this has prompted the need for a MPH medicine authorised with the initiation of treatment in adults. One sustained release MPH medicine was authorised (9 March 2014) through a work sharing procedure DE/H/XXXX/WS/056 (Ritalin LA), to include the initiation of treatment in adults. In addition, 5 strengths of Medikinet adult (instant release MPH) have been authorised in DE. As a consequence, information concerning authorised adult patient exposure will be difficult to determine, similarly for off-label use (see section 1.3.3). It is important to recognise that for these adults, pre-existence of ADHD during childhood needs to be determined by a specialist according to DSM 5 criteria.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

Cumulatively until the DLP 31 October 2015, various actions were taken outside the EU with the inclusion of additional adverse events to product information in relevant countries.

The following table provides a cumulative list of significant actions taken for safety for MPH products within the EU. The following table is also reproduced in the PSUR for OROS-MPH.

Cumulative List of Significant Actions Taken for Safety Reasons

Country(ies)/Region	Action Taken	Comment	Date
European Union	Submission of the following final study report to the Medicines and Healthcare Products Regulatory Agency (MHRA): Hammerness, P., et al (2014) Impact of long-term treatment with OROS methylphenidate on pubertal development in adolescents with	Within the framework of the Article 31 Referral for all methylphenidate (MPH)-containing products (EC decision date 27 May 2009) the Company was required to submit the final published study report of a two-year, long-term, open-label, prospective investigator initiated study (IIS) to	Jun 2014

Country(ies)/Region	Action Taken	Comment	Date
	ADHD. Open Journal of Psychiatry, 4, 147-152.[4]	monitor pubertal development to determine whether methylphenidate has any effect on adolescent growth and development	
EU	In 26 Sep 2012 WS PSUR FAR MHRA requested the MAHs* to address Signals for Spina Bifida/Neural Tube Defects from the World Health Organisation (WHO) Collaborating Centre for the European Surveillance of Congenital Anomalies (EUROCAT)	To obtain and evaluate data to further investigate the signal for spina bifida /neural tube defects from EUROCAT	Ongoing
EU	Long-term effects: MAHs to monitor the European long-term observational study of methylphenidate in children and adolescents, Attention Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) funded through the EC 7th framework.	MAHs to monitor ongoing external research efforts including ADDUCE	Ongoing
EU	Article 31 referral FUM: Evaluate final study report MTA Study. "Effects of stimulant medication on growth in the MTA (Multimodal Treatment Study of ADHD)" follow-up, carried out by the MTA Cooperative Group.	Evaluate MTA Study. "Effects of stimulant medication on growth in the MTA (Multimodal Treatment Study of ADHD)"	Ongoing (MTA study report not yet published)
EU	Article 31 referral FUM: Drug Utilisation Studies of retrospective data on annual review basis for five years (2008-2012)	Submit Drug Utilisation Studies for 5 consecutive years (Dec 2009 (2008 data); Dec 2010 (2009 data); Dec 2011 (2010 data); Dec 2012 (2011 data); Dec 2013 (2012 data)	Jan 2014
EU	Article 31 referral FUM:	Agency agreement for	24 Sep2012

Country(ies)/Region	Action Taken	Comment	Date
	proposals for fully harmonised risk minimisation tools including a "physician's guide to prescribing" and checklists for actions "before prescribing" and for "ongoing monitoring"	pan-EU core English educational tools (physician's guide to prescribing" and checklists for action National submission of educational tools ongoing	National submissions and approvals ongoing
France	The French Health Authority (ANSM) posted a Patient Information Sheet (PIS) communication on its website. ANSM requested MAHs to conduct and submit in vitro study results to evaluate effects of methylphenidate and its metabolite Ritalin acid (PPAA) on 5HT2B receptors.	ANSM website published PIS MAHs submitted methylphenidate/5HT2B receptor study report and follow-up report	17 Jul 2013 Jun 2013 and Dec 2013
France	Reminder to prescribers and pharmacists concerning conditions of prescription, dispensing and use of methylphenidate and recommendations for monitoring ADRs (adverse drug reactions)	Dear Healthcare Professional Letter	25 Sep2012
EU	European Commission decision for an Article 31 referral procedure (2001/83/EC as amended) as a result of concerns regarding cardiovascular adverse events including sudden death, cerebrovascular disorders, and psychiatric disorders	Core methylphenidate SmPC (Summary of product Characteristics) and list of Conditions of the Marketing Authorisation (i.e., follow-up measures)	27 May 2009
EU	Article 31 referral FUM: Harmonised EU Package Leaflet	Approval of variation to introduce core methylphenidate Package leaflet text (UK/H/0544/001/II/055)	22 Dec 2009

Country(ies)/Region	Action Taken	Comment	Date
EU	Article 31 referral FUM: Evaluation of the final report published by FDA/AHRQ/Vanderbilt University (to address cardiovascular and cerebrovascular effect risks)	Submit evaluation of study report	26 Apr 2012
EU	Article 31 referral FUM: Evaluation of Novartis studies investigating cytogenetic effects in children treated with methylphenidate (Study CRIT124D2201 and Study NCT 00341029) to address the important potential risk of carcinogenicity	Submit evaluation of Study CRIT124D2201 and Study NCT 00341029	30 Mar2009
EU	Article 31 referral FUM: Make available the final study report 2-year, long-term, open-label, prospective investigator initiated study in the US on 150 adolescents (12-17 years) to monitor pubertal development to determine whether methylphenidate has any effect on adolescent growth and development	Submit manuscript for IIS Study (Does Long term Treatment with OROS Methylphenidate Adversely Impact Pubertal Development in Adolescents with ADHD?)	12 Sep2012
EU	Article 31 referral FUM: MAH meta-analysis of the risk of suicidality associated with the use of methylphenidate on the basis of clinical trial data available to MAHs (to address psychiatric effects risks)	Submit meta-analysis of the risk of suicidality	9 Dec 2011
EU	Article 31 referral FUM: MAH feasibility assessment for a long-term safety study to examine adverse cognitive and psychiatric outcomes (to address long-term use effects risk)	Submit feasibility report for a long-term safety study	9 Dec 2009

Country(ies)/Region	Action Taken	Comment	Date
EU	Article 31 referral FUM: Submit once yearly PSURs for 3 years (2009-2011)	Submit annual PSURs for 3 consecutive years	9 Dec2011
EU	Article 31 referral FUM: Implement common core safety specification of identified and potential risks	Implement core list of risks and submit CONCERTA RMP (RMP version 2 dated 23 Nov 2009)	9 Dec 2009

*MAHs refers to the Marketing Authorisation Holders of methylphenidate-containing medicines in the EU that were the subject of the Article 31 referral dated 27 May 2009: Janssen, Novartis, Shire, Medice and Laboratorios Rubio

Study CRIT124D2201 "An open label, behavioral treatment controlled evaluation of the effects of extended release methylphenidate (Ritalin LA) on the frequency of cytogenetic abnormalities in children 6-12 years old with attention deficit hyperactivity disorder". Study NCT 00341029 "Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed With Attention Deficit/Hyperactivity Disorder (ADHD) and Treated With Methylphenidate or Adderall", carried out by US National Institute of Environmental Health Sciences in collaboration with FDA

During the period 01 Nov 2014 to 31 Oct 2015, the following table outlines actions that were taken for safety reasons outside the EU. With the exception of Rhabdomyolysis and priapism, these AEs are reflected in the EU product information.

Actions taken outside Europe

Description of the action(s) taken during the reporting interval	Action(s) taken by	Status of the action(s) taken	Reason for action taken
On 17 Apr 2015, US-Food and Drug Administration (FDA) issued a supplement approval for the addition of "rhabdomyolysis" to the Adverse Reactions-Post marketing Experience and over dosage sections of USPI.	US-FDA	Approved and effective on 17 Apr 2015	Health Authority (HA) request
Following US- FDA issued an announcement related to methylphenidate, Costa Rica, Hong Kong and Thailand labels were amended to add a new sub section on 'priapism' under section 'Warnings and Precautions'	Costa Rica HA; Department of Health, Hong Kong Thailand FDA	Approved and effective	Health Authority requests, based on safety information with FDA conclusions of the review published on 17 Dec 2013 on FDA website.
Following class labelling request from Canada HA, below changes incorporated to the PI: Section **Warnings**: • Additional information regarding the emergence of new psychotic or manic symptoms, aggression, suicidality and other psychiatric events has been added under sub section Psychiatric conditions. •Addition of new paragraphs regarding Priapism and Peripheral Vasculopathy, Including Raynaud's Phenomenon	Health Canada	Approved and effective	Health Canada requested a class-labelling change for all stimulant ADHD drugs (amphetamines and methylphenidate hydrochloride drugs).
On 21 Apr 2015, Novartis along with other two MAHs of methylphenidate hydrochloride in Canada (Janssen Inc. and Purdue Pharma) issued Dear Health Care Provide Letter (appendix 1D) regarding methylphenidate hydrochloride and Priapism.	Health Canada	Approved and effective	Health Authority request
On 30 Mar 2015, Health Canada issued important safety information for drugs used in the management of ADHD including Ritalin Package Insert to update with stronger and clearer warnings on the risk of suicidal thoughts and behaviors.	Health Canada	Approved and effective	Health Authority request

Lead Member State/PRAC assessment comment: The cumulative table is an accurate representation of events taken for safety concerns concerning MPH. The recent updates to the reference product safety

information in Canada, Hong Kong, Costa Rica, and Thailand concerning the ADR for priapism is undergoing continual monitoring through the PSURs in the EU (see section 2.3). In terms of the serious ADR of rhabdomyolysis, a cumulative review will be required (see section 2.3).

1.3.2. Changes to reference safety information

The reference safety Information for the reference product (Ritalin), Equasym, and OROS-MPH is the company Core Data Sheet (CDS) dated 7 January 2014 and 25 August 2015 respectively.

OROS-MPH; the following changes were made in the CDS during the period 1 November 2014 to 31 October 2015:

14 April 2015

- **Contraindications:** Deletion of contraindication in patients with a family history or diagnosis of Tourette's syndrome.
- **Warnings and Precautions – Motor and verbal tics, and worsening of Tourette's syndrome:** Addition of Tourette's syndrome to existing warning for motor and verbal tics; revision to guidance on patient management.

25 August 2015

- **Adverse Reactions – Postmarketing Data:**
  - Addition of new adverse reactions under the *Hepatobiliary disorders* System Organ Class (SOC): *Hepatocellular injury, Acute hepatic failure*.
  - Relocation of existing adverse reactions from the *Investigations* SOC to the *Hepatobiliary disorders* SOC: *Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased*.

For alternative MPH MAs the Summary Product characteristics (SmPC) act as the reference safety information.

Lead Member State/PRAC assessment comment: Following the article 31 referral and during prior WS procedures, a core Safety Information Profile was required and agreed by all MAHs. As a result, the SmPCs contain harmonised warnings and precautions, and are inclusive of a relatively harmonised list of undesirable events. Educational materials are required for all MPH products in order to inform both healthcare professionals (HCPs) and patients of the risks and to provide the HCPs with checklists for use during the initiation of treatment, and for continual monitoring. The educational materials are also detailed in the RMPs.

The CDS is not an exact replica of the SmPC However, the SmPC should reflect the safety information contained within the CDS and any omissions discussed. Information concerning Tourette's syndrome is in line with information contained within the core harmonised SmPC. The emergence or worsening of Tourette's and or tics is known for all stimulants like MPH and is reflected in the SmPC in section 4.4 'warnings and precautions'. Healthcare professionals are advised to monitor patients for these events and regularly review treatment. This information is also highlighted in educational materials for healthcare professionals and information for patients. During the article 31 referral 2008 it was considered that Tourette's or motor tics are not considered a contraindication and that a warning is more applicable to the clinical presentation in patients with ADHD.

The location of hepatobiliary disorders placed under the SOC hepatobiliary disorders. Raised hepatic enzymes, will be detected during investigations and are indicators of potential hepatic disorders. Therefore it is important that this information is also contained within the SOC investigations in the SmPC. The SmPC reflects raised hepatic enzymes in the SOC hepatobiliary disorders and investigations, and therefore this is sufficient.

The SmPC also includes the adverse reaction of hepatic coma in the SOC hepatobiliary disorders and as a potential reaction attributed to overdose. MedDRA v19 lists both acute hepatic failure and Hepatic coma as a LLT of the HLT hepatic failure and associated disorders and therefore hepatic failure may be considered as a more appropriate description for both reactions. Hepatocellular injury is listed as a lower level PT of the HLT Hepatocellular damage and hepatitis NEC. The addition of the adverse reaction of hepatocellular injury is further discussed in section2.3.

1.3.3. Estimated exposure and use patterns

Subject Exposure in Clinical trials

Ritalin LA

Cumulatively [redacted] patients were exposed to Ritalin LA through 15 phase I to IV clinical studies, amounting to a total overall exposure of [redacted]. Stratification by age is provided in the following table;

Table 5-2 Cumulative subject exposure to Ritalin LA from completed clinical trials by age and sex*

Age Range (years)	Number of subjects		
	Male	Female	Total
6-12 Y	[redacted]	[redacted]	[redacted]
13-17 Y	[redacted]	[redacted]	[redacted]
>=18 Y	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
*Data from completed trials as of 31 Oct 2015.			

OROS-MPH

Cumulatively, over a period of approximately 20 years and 21 clinical trials, [redacted] were exposed to OROS-MPH. Stratification by age is provided in the following table;

Table 4: Cumulative Subject Exposure to OROS® Methylphenidate Hydrochloride From Completed Clinical Trials by Age and Sex

Age Range (Years)	Number of Subjects		
	Male	Female	Total
<6	[redacted]	[redacted]	[redacted]
6 to 12	[redacted]	[redacted]	[redacted]
13 to 17	[redacted]	[redacted]	[redacted]
18 to 35	[redacted]	[redacted]	[redacted]
36 to 49	[redacted]	[redacted]	[redacted]
50 to 66	[redacted]	[redacted]	[redacted]
Missing[a]	[redacted]	[redacted]	[redacted]

Note: Data from completed trials as of 31 October 2015
Key: OROS= Osmotic Controlled-Release Oral Delivery System.
a: One subject from study 12-101 had missing value for sex.

Lead Member State/PRAC assessment comment: Within the period 1 November 2013 – 31 October 2014, the PSUR for MPH provided information that cumulative subject exposure during clinical trials was only provided for Ritalin LA since the beginning of the development programme. As MPH has been

authorised for a considerable number of years, complete datasets are not available for the original studies of MPH. Generic MPH formulations would also have a low number of subjects exposed as these would be taken from bioequivalence studies only.

Post-authorisation Exposure

Ritalin

The following table summarises the post-authorisation exposure presented within the annual reporting periods from 2011:

PSUR Number	#11	#12	#13	#14
Reporting period	1 Nov 2011 – 31 Oct 2012	1 Nov 2012 – 31 Oct 2013	1 Nov 2013 – 31 Oct 2014	1 Nov 2014 – 31 Oct 2015
Sales volume (kg)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Calculations are based upon the [redacted] The numbers above refer to sales of MPH from [redacted].

Cumulative sales data since first registration is not possible. Sales data are only available from 1998. Between Jan 1998 and Oct 2015, the cumulative patient exposure of the product is estimated to be [redacted].

Medikinet

Calculation of patient exposure from cumulative sales from marketing authorisation using [redacted], an estimated [redacted] and [redacted].

Medikinet adult

Calculation of patient exposure from cumulative sales from marketing authorisation using [redacted], an estimated [redacted] dosage days and [redacted].

OROS –MPH

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. OROS-MPH should be taken once per day. The average month [redacted]. Therefore, [redacted].

Based on the [redacted] of OROS-MPH distributed by the Company (from 01 November 2014 to 31 October 2015), the estimated [redacted]. The exposure in the current period is [redacted] than the previous period (01 October 2013 to 30 September 2014) due to recent reporting in generic MPH in the US.

For the current reporting period, exposure is broken down by region in the following table;

Table 7: Exposure to OROS® Methylphenidate Hydrochloride (01November 2014 to 31 October 2015)[a]

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

Key: HCl= Hydrochloride; OROS®= Osmotic Controlled-Release Oral Delivery System; UK= United Kingdom.

a: [redacted]

b: Current data for North America now includes [redacted]

c: Rest of World does [redacted] in this table since it has been reported separately.

Cumulative exposure. Based on the [redacted] OROS-MPH distributed by the Company (from launch to 31 October 2015), the estimated [redacted].

Lead Member State/PRAC assessment comment: Post-authorisation patient exposure for MPH (inclusive of Ritalin, Ritalin LA and generic MPH medicines held by Novartis and Sandoz) [redacted] for each annual reporting period.

Whilst for OROS-MPH, [redacted], in the [redacted] exposure in [redacted]. However, this is not reflected in all countries. A breakdown of exposure data per country since 2011 (as shown in the table below) has been provided in the annual PSURs and shows that for those countries with [redacted], with the [redacted], exposure has either remained [redacted].

In order to make a comparison with previous reporting periods, the following table has been constructed by the Assessor from data presented in annual reporting periods from 2011 to 2015:

Region	Country	Patient years in Reporting Period 2011-2012	Patient Years in Reporting Period 2012-2013	Patient Years in Reporting Period 2013-2014	Patient Years in Reporting Period 2014-2015
European Union	Austria				
	Belgium				
	Bulgaria				
	Croatia*	-	-		
	Cyprus				
	Czechia				
	Denmark				
	Estonia				
	Finland				
	France				
	Germany				
	Greece				
	Ireland				
	Latvia				
	Lithuania				
	Malta				
	Netherlands				
	Poland				
	Portugal				
	Romania				
	Slovakia				
	Slovenia				
	Spain				
	Sweden				
	UK				
Subtotal					
North America					
Rest of World					

Switzerland	Switzerland	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]

*The calculated patient years for Croatia were initially added to the totals representing the 'rest of the world'. Given that the subsequent calculations [redacted] it is [redacted] the totals for Europe. [redacted].

However, it should be borne in mind that interpretation of these figures has limitations. The calculated number of patient years of exposure will also be dependent upon the diagnosed patient population per country. Diagnosis of ADHD was guided by ICD 10 and DSM IV until May 2013 when diagnosis was guided by ICD 10 and the updated DSM 5. Comparisons of exposure between countries are not representative of patient prescribing per country. Patient exposure of the originator product may be affected by the introduction of alternative generic longer acting MPH products.

National clinical guidance would have an effect on the recommended pharmaceutical medicine to be used in the treatment of any patients diagnosed with ADHD. For the UK, national patient prescribing has moved towards the use of generic products. The introduction of DSM 5 and NICE guidance has increased potential patient prescribing to those diagnosed with ADHD in adults not formerly identified during childhood. Therefore a move towards increased generic prescribing could be counteracted by increased prescribing to adults with ADHD. At this time, the consequences of the amendments to DSM are not obvious.

An additional stratification is made for gender and age as a percentage of prescription (Rx) sales taken from IMS data where possible.

Table 9: Post-Marketing (Non-Study) Exposure for OROS® Methylphenidate Hydrochloride by Age Group in Europe (01 July 2012 to 30 June 2015)

Age Groups (Years)[a]	EU[b] (4,385,235 R_x[c])
0-17 18-35 36-64 ≥65	[redacted]

Key: EU= European Union; OROS= Osmotic Controlled-Release Oral Delivery System; R_x= Prescription; UK= United Kingdom.

a: Regional R_x data by age are only available for the last 3 years ending 30 June 2015.

b: Data stratified by age are only available [redacted]

c: R_x= Prescriptions, includes retail channels.

Table 11: Post-Marketing (Non-Study) Exposure for OROS® Methylphenidate Hydrochloride by Gender (01 July 2012 to 30 June 2015)

	Females[a]	Males[a]	Patient Gender Unidentified[a]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
UK	[redacted]	[redacted]	[redacted]
Canada	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
US	[redacted]	[redacted]	[redacted]

Key: HCl= Hydrochloride; OROS= Osmotic Controlled-Release Oral Delivery System; R_x= Prescription; UK= United Kingdom; US= United States

a: Regional R_x data by age are only available for the last 3 years ending 30 June 2015. Data are [redacted]

b: R_x= prescriptions, includes retail channels.

Lead Member State/PRAC assessment comment: The stratification of Post-authorisation patient exposure for OROS-MPH shows that the predominant patient population is males under the age of 18 years. This is as previously described for patients with ADHD. As patients can continue to be treated into adulthood, it is not surprising that there will be a certain percentage of adults that are prescribed with OROS-MPH. However, it cannot be determined from this data, whether prescribing has been initiated in childhood or in adulthood. It is more likely that adults >35 years will have had initiation of treatment for ADHD during adulthood, which is considered to be off-label for OROS-MPH, but not for all MPH medicines (see section 1.3.5).

1.3.4. Data in summary tabulations

Overview of safety reports: Ritalin

	01 Nov 2011 to 31 Oct 2012	01 Nov 2012 to 31 Oct 2013	01 Nov 2013 to 31 Oct 2014	01 Nov 2014 to 31 Oct 2015	Cumulative
Suspected cases from post-marketing data sources					
Serious and non-serious cases from spontaneous reporting, incl literature	1660	3268	1184	1114	20533**
Serious cases from solicited post-marketing data sources	3	11	53	55*	200*

IMP – investigational product

*not assessable cases included

** cases with unknown seriousness included

SAEs from Clinical Trials

Cumulative to 31 October 2015		
System Organ Class	**MPH**	**OROS-MPH**
Cardiac disorders	2	1
blood	0	5
Ear and labyrinth disorders	2	1
Endocrine	1	0
Eye	0	1
Gastrointestinal disorders	2	13
General disorders and administration site conditions	2	5
Hepatobiliary disorders	2	0
Immune system disorders		0
Infections and infestations	2	28
Injury, poisoning and procedural complications	4	14
Metabolism and nutrition disorders	0	7
Musculoskeletal and connective tissue disorders	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0
Nervous system disorders	3	15
Pregnancy, puerperium and perinatal conditions	1	0
Psychiatric disorders	7	45
Renal and urinary disorders	1	3
Reproductive system and breast disorders	1	1
Respiratory, thoracic and mediastinal disorders	2	9
Skin	0	1
Surgical and medical procedures	1	2
Vascular disorders	1	5
Total	**36**	**158**

Lead Member State/PRAC assessment comment: The data in the summary table above has been extracted from the appendices for the originator product 'Ritalin' by the assessor. As expected the largest number of serious reports arising from clinical trials originates from the SOC psychiatric disorders.

Cumulative Post authorisation Spontaneous Reports

	Cumulative Total to 31 October 2015	
System Organ Class (SOC)	**MPH**	**OROS-MPH**
Blood and lymphatic system disorders	**606**	**249**
Cardiac disorders	**1298**	**1155**
Congenital and familial and genetic disorders	**131**	**89**
Ear and labyrinth disorders	**155**	**170**

Endocrine disorders	**105**	**88**
Eye disorders	**1062**	**1204**
Gastrointestinal disorders	**3212**	**3449**
General disorders and administration site conditions	**7427**	**7261**
Hepatobiliary disorders	**134**	**101**
Immune system disorders	**196**	**147**
Infections and infestations	**479**	**411**
Injury poisoning and procedural complications	**2650**	**4029**
Investigations	**2878**	**2781**
Metabolism and nutrition disorders	**1681**	**2321**
Musculoskeletal and connective tissue disorders	**1024**	**1031**
Neoplasms benign, malignant and unspecified	**84**	**51**
Nervous system disorders	**7042**	**5379**
Pregnancy, puerperium and perinatal conditions	**116**	**55**
Psychiatric disorders	**11601**	**11413**
Renal and urinary disorders	**399**	**379**
Reproductive system and breast disorders	**383**	**391**
Respiratory thoracic and mediastinal disorders	**855**	**881**
Social circumstances	**178**	**530**
Skin and subcutaneous tissue disorders	**2505**	**2239**
Surgical and medical procedure	**127**	**145**
Vascular disorders	**733**	**629**
Total	**47061**	**46578**

Lead Member State/PRAC assessment comment: The data in the summary table above has been extracted from the appendices for the originator product 'Ritalin' and OROS-MPH by the assessor. Both of the summary tables of the relevant PSURs included PTs coded using MedDRA v18.1.

A high number of general disorders are reported, the majority of which concerns 'drug ineffective'. However, this must be taken in the context of dose titration, and/or the severity of ADHD requiring combination therapy, or substitution to an alternative pharmacotherapy that can only be prescribed when all other pharmacological agents have been tried. MPH is first line, therefore will not be the most effective treatment for all ADHD patients.

As expected the larger number of reports arising from spontaneous reporting, originate from the SOCs psychiatric disorders and nervous system disorders. These are known to predominate in this patient population, and therefore are not unusual. Of interest, for Ritalin/OROS-MPH, within the SOC psychiatric disorders, cumulatively there are 21/36 reports of self-injurious behaviour; 19/29 intentional self-injury; 1/11 Dermatillomania; and 4/14 reports of self-injurious ideation. It is known that concomitant psychoses may be apparent in patients with ADHD. Similarly, ADHD medicines may be associated with emergent underlying psychoses. The use of MPH and OROS-MPH is also contraindicated in patients with depression or suicidal tendencies. Whilst overall the numbers of self-injurious reports may be low, self-injury can have serious consequences. Therefore, the MAHs are recommended to undertake a review of all cases of self-injurious behaviour for inclusion in the next PSUR.

In the SOC Hepatobiliary disorders, 134 reports were received for Ritalin products. The majority are in relation to hepatitis related PTs and jaundice (26 reports). Drug induced liver injury has been further reviewed by the MAH for OROS-MPH and is considered by the MAH to be an important identified risk (see section 2.3).

1.3.5. Findings from clinical trials and other sources

Completed clinical Trials

Ritalin: There were no CTs completed during the reporting interval 2013 – 2015 (PSURs 13 and 14).

During the period 2012 – 2013 (PSUR 12), one clinical trial was completed:

RIT124D2302 was a 40-week, randomized, double-blind, placebo-controlled, multicentre efficacy and safety study of Ritalin LA in the treatment of adult patients with childhood-onset of ADHD.

The primary objectives of the study were:

- To confirm the clinically effective and safe dose range of Ritalin LA in adults with childhood onset ADHD as measured by the change from Baseline to the end of a 9-week, fixed-dose treatment period (period 1) in DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS) total score and evaluate improvement in functional impairment as measured by change from baseline in total score on the Sheehan Disability Scale (SDS).
- To evaluate the maintenance of effect of Ritalin LA in adults with childhood onset ADHD as measured by the percentage of Ritalin LA vs. Placebo treatment failures at the end of a six month treatment withdrawal period (period 3), according to DSM-IV ADHD RS scores.

Ritalin LA was found to be effective and safe in the treatment of ADHD in adults, in a dose range including 40-80 mg MPH daily. The results were consistently in favour of Ritalin LA over placebo across all assessments.

No unexpected AEs were observed. The adverse effect profile of Ritalin LA in the treatment of adults with ADHD was similar to that previously observed in the treatment of children with ADHD.

Ongoing Clinical Trials

There were no ongoing clinical trials during the reporting period 2012 to 2015 (PSURs 12, 13 and 14)

Non-interventional studies

There was no relevant safety information or information with potential impact on benefit risk.
A DUS to examine retrospective usage of all MPH products (including IR, 'long-acting' and OROS-MPH) over a five year period from 1 January 2008 to 31 December 2012, was concluded and the findings presented in the PSUR covering the period 2012 - 2013. The DUS was undertaken on behalf of Novartis, Janssen Pharmaceutica N.V., Shire, Medice and Laboratorios Rubio S.A.

In most countries the percentage of prescriptions given to patients between 6 and 18 years old was [redacted] for the whole period; however, [redacted] this average [redacted] and in [redacted]. For the total 5 years period, hyperkinetic disorders (ICD 10 - F90 diagnosis) was the most frequent diagnosis associated with methylphenidate prescriptions in all countries. Average daily dose (ADD) was generally within the maximum recommended dose in all countries [redacted]

[redacted]. However, the [redacted]. Mean treatment durations were [redacted]. These durations included drug holidays up to approximately 8 weeks. Whilst the mean duration of treatment [redacted].

Considering all the data, and despite the data limitations addressed, the results of this drug utilisation study in Europe over 5 years indicate that methylphenidate is prescribed largely within the recommendations of the SPC.

Lead Member State/PRAC assessment comment: Comparisons between countries are not possible owing to the different methods of data collection. However, the trends that can be seen are generally reflected in all countries. The numbers of prescriptions overall have increased, whereas the number of prescriptions to patients between 6 -18 years [redacted]. [redacted] could be reflective of the [redacted] over time. The [redacted] within ages 6 – 18 years [redacted], however in [redacted]. This is of note as this was occurring prior to the amendment of DSM IV to DSM 5. This may be reflective of the increased availability of alternative medicines such as atomoxetine, or an increased prescribing to patients outside this age range. Certainly this study shows that there has been a greater prescribing to adult patients over time. It can be identified in some countries that prescribing was initiated during adulthood. During this whole period, there was a significant amount of studies, discussion and debate worldwide, including the EU, which eventually led to the amendment of the DSM. Hence the increasing prescribing is not surprising. The introduction of the amended DSM therefore was a much needed, considered and agreed amendment providing for a unification of diagnoses and clinical guidance.

During this period, the continued use of MPH into adulthood was accepted. Some MPH products are now authorised for the initiation of prescribing to adults which will have a further impact on prescribing patterns within the EU. Hence it is likely that further amendments in prescribing patterns will occur, including usage in adult patients. For some MAs, the initiation of treatment will be considered to be off-label; however local clinical guidance will also impact on these changes.

The use of MPH for off-label indications other than ADHD will hopefully become clearer with time and a more detailed analysis of the risks and safety can be made when MPH is used outside the indication of ADHD where benefit has not been proven.

FR Comments

A drug utilization study was requested following the article 31 referral. Novartis provided the fifth and final report of this study as part of the PSUR 12 Ritalin covering the period 01-Nov-2012 to 31-Oct-2013. This DUS study was developed to provide data and information on how MPH is prescribed under conditions of routine medical practice, including off label use. To our knowledge, as no PSUR WS AR circulated for this PSUR, the results of this study have not been assessed.

Off label use is mentioned as a safety concerns (missing information). The results of the drug utilization study should be assessed in order to qualify off label use with methylphenidate as requested by the article 31 conclusions.

FR ask that an overview of the progress of each study (completed and ongoing) requested by the CHMP following the article 31 procedure and includes in the core RMP (i.e. MTA long

term treatment study, DUS, FDA cardiovascular epidemiology study, meta-analysis on suicidality) be made as part of this PSUSA procedure.

Lead Member State/PRAC assessment comment:

The MTA long-term treatment study; This study has been monitored through successive RMPs. The primary report was published in 1999, with expectations that further publications would follow. No further study reports have been published on this long-term study since 2009.

DUS

The LMS apologises for the omission to circulate the complete assessment of the Final DUS. The full assessment is therefore attached in appendix II with further comments of the LMS included throughout.

The FDA cardiovascular epidemiology study was reviewed by the PhVWP in November 2011 and December 2011. The PhVWP endorsed the conclusions of the study, that serious end stage cardiovascular disorders including sudden death were extremely rare. The few reports of sudden death were associated with congenital disorders and haemodynamically significant congenital heart disease is includedas a contraindication in section 4.3 of the SmPC, with further warnings in section 4.4 of the SmPC.

Suicidality

An assessment of the meta-analysis of suicidality was undertaken following the submission of the final study report 2011. The assessment was as follows:

Suicidality Meta-analysis

The MAHs submitted a meta-analysis of suicide-related events in placebo-controlled trials of methylphenidate for treatment of children with ADHD. This was undertaken by Life Science Services on behalf of the 5 MAHs, report dated 30 Nov 2011. The objective was to evaluate the risk of suicide-relate events during treatment with MPH relative to placebo in children and adolescents with ADHD. The primary analysis was at an individual patient level from randomized, placebo controlled trials conducted by the MAHs. The secondary analysis was at a study-level from randomised, placebo controlled trials conducted by the MAH or other sponsors identified through a bibliographic search in several electronic sources.

In the primary analysis, potential suicide or self-harm-related events were identified and classified according to the Columbia Classification Algorithm of suicide assessment (C-CASA) as follows;

- Code 1 – completed suicide
- Code 2 – suicide attempt
- Code 3 – Preparatory acts toward imminent suicidal behaviour
- Code 4 – suicidal ideation
- Code 5 – self-injurious behaviour, intent unknown
- Code 6 – Not enough information, fatal
- Code 7 - self-injurious behaviour, no suicidal intent
- Code 8 – Other: accident; psychiatric; medical
- Code 9 – Not enough information, nonfatal

Categorisation was undertaken by two independent reviewers experienced in the use of C-CASA. A third reviewer categorised those where there was disagreement between the initial two reviewers. End-point was the risk of a suicide-related events, therefore four outcomes were analysed: suicidal ideation (code 4), suicidal behaviour (codes 1-3) suicidal behaviour or ideation (codes 1-4) and possible suicidal behaviour or ideation (codes 1-6, 9).

Studies with no events in any arm would be excluded in the analysis, therefore a sensitivity analysis was conducted to include all available data including studies with no events, using risk differences and a fixed effect model.

Results were presented as Forest Plots. In the primary and secondary analysis, Odds Ratios (ORs) >1 indicate an increased risk for MPH whereas ORs < 1 indicate a reduced risk for MPH. Risk Differences (RDs)>0 indicate an increased risk for MPH and RDs<0 a decreased risk.

In the secondary analysis, an overall OR or RD was not calculated owing for the potential for bias.
In the secondary analysis the events in the non-MAH sponsored studies were not adjudicated as individual patient's level data were not available. Because of the lack of adjudication in the non-MAH-sponsored studies and the small number of events in all the trials, the outcome was considered to be any event with CASA classification of codes 1-9.

Primary analysis
For the primary analysis, 22 studies were identified meeting the inclusion criteria of minimum duration 7 days, minimum number of participants n=10, and placebo controlled. In total 2846 patients (1838 MOH and 1008 placebo) were identified and evaluated. All but three were conducted in the US and Canada; 2 in Germany and 1 in Australia. Total daily dose ranged from 5 to 60mg (IR equivalent) across the studies. All paediatric patients aged 5 – 17 years met DSM-IV criteria for ADHD. 63-89% of the study population were male.

A total of 22 patients (12 MPH and 10 on placebo) had an event of interest, however 21 were categorised to C_CASA code 8. One patient from a placebo arm, described an event coded as code 5 related to self-injurious behaviour intent unknown. None of the trials had events that were categorised as suicidal ideation (code 4) suicidal behaviour (codes 1 to 3) in any of the arms. Therefore a meta-analysis was conducted only for "possible suicidal behaviour or ideation (codes 1-6, 9). Only one trial had an event in this range. The trial had 90 subjects exposed to MPH and 42 on placebo. The single event occurred in a patient on placebo.

The overall estimated OR for MPH vs placebo was 0.04 (95%CI 0.001, 2.90). Therefore MPH was not associated with a significant increased risk. In the sensitivity analysis (zero event trials), all 22 trials were included to calculate RD. The results were homogenous with an overall calculated RD -0.001 (-0.009, 0.007). This supports the finding that MPH was not associated with an increased risk of possible suicide behaviour or ideation relative to placebo.

Secondary analysis
Following a literature search, 93 potential studies were identified as potentially relevant, however 92 were rejected owing to: no events of interest (51), no safety data (31), not all participants had an ADHD diagnosis (2), study sponsored by one of the MAHs (2), meta-analysis (2) treatment duration less than 7 days (1) no placebo control (1), literature review (1) event of interest did not occur during placebo controlled phase (1). The same MAH sponsored studies were included in the secondary analysis.
The single non-MAH sponsored studies included involved 65 patients (58M, 7F), aged between 8 – 11years, a 5 way DB cross-over, 13 patients on placebo and 52 MPH. this study compared 4 total daily doses of MPH (5, 10, 15 and 20mg/day) vs placebo. One patient reported 'more self-harm behaviours in the 15mg MPH period. This event was also reported at baseline by one other patient. No events of interest were reported in the placebo period.

Owing to the lack of adjudication in the non-MAH sponsored trial, and the low number of events, the outcome considered any event of interest coded 1-9). Eleven trials had events of interest. 13 events in 1173 subjects exposed to MPH and 10 events in 484 subjects exposed to placebo. Twelve of the MPH events were classed as code 8 and one as self-injurious behaviour. Of the placebo events, 9 were classed as code 8 and one code 5. The estimated overall odds ratio for MPH vs placebo was 0.61

(0.25,1.49). Therefore MPH is not associated with a significant risk of any event of interest including possible suicidal behaviour or ideation, self-harm or other events relative to placebo.

The sensitivity analysis including trials with no events in any arm provided a calculation of RD as 0.004 (-0.0014, 0.007). This supports the finding that MPH was not associated with an increased risk of any event of interest including suicidal behaviour etc.

MAH conclusion
The risk of suicidal or self-harm-related events with MPH was low. Without adjusting for differences among trials, 0.69% of the MPH patients had an event of interest and 0.98% of the placebo patients had an event of interest. Based on these findings the benefit risk profile for MPH remains favourable with respect to its potential effect on suicidal behaviour and ideation, and self-injurious behaviour during treatment of children and adolescents with ADHD.

Lead Member State / PRAC assessment comment; The MAHs have undertaken a detailed meta-analysis of sponsored studies. The results of this analysis clearly indicate that there is no difference between MPH treated patients and placebo treated patients. These results are encouraging, however, it should be noted that the emergence of suicide-related behaviour during the clinical trial situation will potentially be abated owing to the extra attention the patients are receiving as a result of the trial. The SmPC contains warnings concerning suicidal behaviour and underlying conditions prior to treatment with MPH, therefore the SmPC is sufficient. Given the number of spontaneous reports received suicide should continue to be actively monitored and reviewed in subsequent PSURs as commented above.

Other sources
There was no information relevant to the benefit-risk assessment for Ritalin from other trial/study sources that became accessible to Novartis during the reporting interval.

Non-clinical data:
There were no major safety findings for MPH from non-clinical *in vivo* and *in vitro* studies during the reporting interval 01 Nov 2012 to 31 Oct 2015.

No non-clinical trials were conducted for OROS-MPH during the reporting period 01 Nov 2012 to 31 Oct 2015

Literature

The following literature reports were identified;

Ari ME et al (2014) Assessment of cardiovascular risks due to methylphenidate in six months of treatment in children with attention deficit and hyperactivity disorder.

Bange F et al (2014) Cardiovascular risks and management during Attention Deficit Hyperactivity Disorder treatment with methylphenidate.

Bhattacharya SE, Shumsky JS, Waterhouse BD. Attention enhancing effects of methylphenidate are age-dependent. *Exp Gerontol*. 2015:61:1-7.

Dalsgaard S et al (2014) Cardiovascular safety of stimulants in children with attention deficit/hyperactivity disorder: a nationwide prospective cohort study. J Child Adolesc Psychopharmacol. 2014;24(6):302-310.

Dalsgaard S., Kvist A. P., Leckman J. F., Nielsen H. S., Simonsen M. “Cardiovascular safety of psychostimulants in children with adhd: findings from a population based cohort study.” *ADHD Attention Deficit and Hyperactivity Disorders. 2015;*7:S14.

Fischer L.J., Severtson S.G., Dart R.C. Prevalence of serious adverse events by injection or inhalation of prescription stimulants. 2015 Annual Meeting of the North American Congress of Clinical Toxicology, NACCT 2015 San Francisco, CA United States. Conference Start: 20151008 Conference End: 20151012. *Clin Toxicol*. 2015:53(7):660-661

Hammerness PG et al (2011) Adult attention-deficit/hyperactivity disorder treatment and cardiovascular implications.

Huss M., Ginsberg Y., Arngrim T., et al. Efficacy and safety of methylphenidate modified release long-acting after reinstatement of therapy in placebo treated patients. 27th European College of Neuropsychopharmacology, ECNP Congress Berlin Germany. Conference Start: 20141018 Conference End: 20141021. *Eur Neuropsychopharmacol*. 2014:24:S209-S210

Formaterat: Svenska (Sverige)

Karapinar U, Saglam O, Dursun E, Cetin B, Salman N, Sahan M. Sudden hearing loss associated with methylphenidate therapy. *Eur Arch Otorhinolaryngol.* 2014;271(1):199-201

Kelly_ AS_ et al (2014) Cardiac autonomic dysfunction and arterial stiffness among children and adolescents with attention deficit hyperactivity disorder treated with stimulants.

Krueger J et al (2014) First detection of methylphenidate in human fatalities after methylphenidate intake

Lamberti M et al (2015) Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with attention-deficit hyperactivity disorder.

Samuels JA et al (2006) Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial.

MAH's conclusion; There was no new and significant safety published in the peer-reviewed scientific literature or made available as unpublished manuscripts suggestive of new safety signal or impacting the existing risk-benefit ratio for the product.

Lead Member State/PRAC assessment comment: The literature identified in the PSURs confirms the current safety concerns. No new safety concerns have arisen from this literature search. The long term prospective follow-up study undertaken by Dalsgaard provides further information concerning all stimulants in the treatment of ADHD, and the safety concern of the risk of cardiovascular events. This supports the need for enhanced pharmacovigilance and continual monitoring by HCPs throughout treatment, and the need for additional risk minimisation measures by way of educational materials for both HCPs and patients/carers.

Other Periodic report

N/A

Medication Error

Ritalin

Cumulatively, a total of 1742 cases (499 HCP and 1243 non-HCP) were reported to DLP 31 October 2015. Of the 1742 cases, 1283 were reported under the HLGT "Medication Error". The following table gives an overview of the PTs under medication error HLGT reported in these cases:

PT	Number (%) Cumulatively
Wrong technique in product usage process	424 (31.71%)
Incorrect dose administered	187 (13.99%)
Drug administration error	135 (10.1%)
Drug prescribing error	97 (7.26%)
Expired product administered	79 (5.91%)
Incorrect route of drug administration	68 (5.09%)
Drug dose omission	56 (4.19%)
Accidental exposure to product	52 (3.99%)
Drug dispensing error	49 (3.66%)
Medication error	47 (3.52%)
Accidental overdose	30 (2.24%)
Wrong drug administered	29 (2.17%)
Inappropriate schedule of drug administration	27 (2.02%)
Poor quality drug administered	19 (1.42%)
Accidental exposure to product by child	9 (0.67%)
Wrong patient received medication	9 (0.67%)
Incorrect drug dosage form administered	5 (0.37%)
Incorrect dosage administered	3 (0.37%)
Drug dispensed to wrong patient	2 (0.15%)
Incorrect drug administration duration	2 (0.15%)
Product preparation error	2 (0.15%)
Incorrect product storage	2 (0.15%)
Extra dose administered	1 (0.07%)
Incorrect drug administration rate	1 (0.07%)
Drug monitoring procedure not performed	1 (0.07%)
Circumstance or information capable of leading to medication error	1 (0.07%)
Total	**1337**

Of the cumulative total 1742 cases, 453 reported events under the HLT 'Product use issues NEC". An overview of the PTs reported in these cases is summarised in the following table:

Preferred term	Number (Percentage) Cumulatively
Product use issue	332 (72%)
Drug administered to patient of inappropriate age	129 (28%)
Total	**461**

Cumulatively, 6 of the 1742 cases reported events under the MedDRA HLT 'under doses NEC', all non-serious.

MAH conclusion: a review of medication error cases did not reveal use patterns of safety information relevant to the benefit risk assessment to warrant changes to the CDS for Ritalin.

OROS-MPH

The following tables have been compiled by the assessor covering the period 1 November 2011 – 31 October 2015.

The following table is a summary of the number of cases of medication error/maladministration identified per year since 2011;

Reporting period	**Non-serious and serious cases in Reporting Period 2011-2012**	**Non-serious and serious cases in Reporting Period 2012-2013**	**Non-serious and serious cases in Reporting Period 2013-2014**	**Non-serious and serious cases in Reporting Period 2014-2015**	**Cumulative Total from 1 Nov 2011 - 31 Oct 2015.**
Total number of cases identified	131	203	233	177	744

Of these cases, 646 cases were stratified by age. Those that were not stratified, were either follow-ups, reports of multiple cases with no identifiers, or misclassified.

Reporting period	**Non-serious and serious cases in Reporting Period 2011-2012**	**Non-serious and serious cases in Reporting Period 2012-2013**	**Non-serious and serious cases in Reporting Period 2013-2014**	**Non-serious and serious cases in Reporting Period 2014-2015**	**Cumulative Total from 1 Nov 2011 - 31 Oct 2015.**
<18 years	50	78	86	59	273
≥ 18 years	57	57	69	59	242
age not reported	20	34	38	39	131
Total number of stratified cases	127	169	193	157	646

The PTs reported in these cases are summarised as follows (more than one PT may appear in case).

MedDRA Preferred Term (PT)	Non-serious and serious cases in Reporting Period 2011-2012			Non-serious and serious cases in Reporting Period 2012-2013			Non-serious and serious cases in Reporting Period 2013-2014			Non-serious and serious cases in Reporting Period 2014-2015			Cumulative Total 2011 - 2015
Age stratification	**<18 years**	**≥ 18 years**	***NR**	**<18 years**	**≥ 18 years**	**NR**	**<18 years**	**≥ 18 years**	**NR**	**<18 years**	**≥ 18 years**	**NR**	
Accidental drug intake by child	1	0	0										**1**
Accidental Exposure to Product	5	0	0	4	1		2	0	0	1	1	3	**17**
Accidental Exposure to Product by child				1			3	0	0	1			**5**
Contraindication to medical treatment				1	1						1		**3**
Drug Administered to patient of inappropriate age	3	4					1	2	0	3			**13**
Drug administration Error	0	0	1	1	1								**3**
Drug dose omission	7	4		16	2	6	10	7	11	5	2	5	**68**
Drug dispensing error				1	2	2	0	1	0	1		1	**8**
Drug name confusion				1									**1**
drug prescribing error	2	9	7			1	19	11	5	10	11	8	**83**
expired drug administered		1				1	1	1	0			2	**6**
extra dose administered							1	0	0				**1**
inappropriate schedule of drug administration	2	3	1	2	7	2	6	3	3	6	7	1	**43**
incorrect dose administered	12	5	3	1			9	9	4	5	8	3	**59**
incorrect drug administration duration		1				1							**2**

incorrect drug dosage form administered					1								**1**
Incorrect route of drug administration		1	1		2		0	0	2		2		**8**
Incorrect storage of drug		2			2								**4**
intentional product misuse											4		**4**
labelled drug-disease interaction medication error										1			**1**
Medication Error			1	7	2	1	1	2	0	1		2	**17**
off label use	6	35	9	18	30	7	14	40	4	2	10	3	**178**
Poor quality drug administered	1	1		2	1	2	5	1	3	1		1	**18**
product use issue										7	21		**28**
treatment noncompliance	8	9		9	4	2	7	7	5	10	5	6	**72**
Under dose	1											1	**2**
wrong drug administered					1								**1**
wrong patient received medication												1	**1**
wrong techniques in drug usage process	6	2	2	11	4	7	17	3	5	12	1	7	**77**
Sub Total	54	77	25	75	61	32	96	87	42	66	73	44	**732**
Total	156			168			225			183			**732**

*NR = Not reported

MAH conclusion: Within a review of medication error/maladministration cases no safety issues were identified and no changes to the reference safety information are required at this time.

Lead Member State/PRAC assessment comment: Ritalin is indicated for the treatment of children, adolescents and adults, and therefore the consideration of 'off-label use' as defined by age is not applicable.

For OROS-MPH, the MAH has listed all events reflecting both medication error and maladministration, therefore includes all case reports of off-label use. For this product, 'off-label use' represents the highest percentage of reports, mainly in relation to ages ≥18 years. For all other PTs there is a greater number of reports in the ages <18 years. This is reflective of the greater exposure in the paediatric age group. 'Off label use' is an identified safety concern. The total number of medication errors has reduced in the reporting period 2014 – 2015. However there are limitations on the interpretation of these annual figures; all numbers will be dependent upon the version of MedDRA that has been used for each reporting period to extract the relevant PTs. Similarly, overall patient exposure has decreased which will result in a lower number of cases reported.

For both Ritalin products and OROS-MPH reveal that the highest PT for medication error is "wrong techniques in drug usage process" the MAH has qualified this PT as examples of; the division of tablets or capsules, or the sprinkling of capsule contents onto food. It is possible that the PT may also be presented in reports as an association with non-compliance, wrong route of administration, and/or prescribing error. Therefore whilst the numbers of this PT appears to be excessive, it should be borne in mind that the application of PTs to an event is also subject to classification by the reporter within the auspices of MedDRA; which itself is updated regularly. Non-compliance by a patient is well known for all treatment therapies. Decisions on the treatment regimen prescribed by the HCP will be guided by the SmPC, local guidance, and clinical decision as determined for the individual need of the patient. The PTs of concern are related to 'accidental exposure' or 'wrong patient received medication'. These PTs appear to be more extensive for the Ritalin products. But again the cumulative numbers for Ritalin cover a wider reporting period. Cumulative numbers have not been summarised for OROS-MPH, although will only represent a shorter reporting period as OROS-MPH is the younger product. It is encouraging to observe that in general the numbers for these PTs are low for the Ritalin products and OROS-MPH.

The conclusions of the MAHs are endorsed.

1.3.6. Lack of efficacy in controlled clinical trials

There were no results from CTs for MPH indicating lack of efficacy which could have a direct impact on subject safety.
There were no results from CTs for OROS-MPH indicating lack of efficacy which could have a direct impact on subject safety.

1.3.7. Late-breaking information

There were no important safety, efficacy and effectiveness findings that arose in the preparation of the PSUR (after the DLP 31 October 2015) for Ritalin.

Since the DLP of 31 October 2015, no late-breaking information has been identified with OROS-MPH.

Medice comments:

We wonder about the listed drug interaction cases of the other MAHs. We received an increase of reports of drug interactions between MPH and Proton-pump inhibitors (PPIs) especially for our long-acting products more recently. Due to this late-breaking and safety relevant information on PSUR data we would like to get your feedback if in case of difference with our MPH long-acting products the recommendation for MEDICE should be to specify in the SmPC and PIL in section 4.3 contraindications: "a history of pronounced anacidity of the stomach with a pH value above 5.5, in therapy with H_2 receptor blockers/proton-pump inhibitors or in antacid therapy"

DE comments:

"Drug interaction" with H_2 receptor blockers, antacids, and proton pump inhibitors
A number of methylphenidate products are formulated as prolonged-release tablets. Depending on the formulation of prolonged-release tablets, these are potentially dependent on the gastric milieu, and release could be affected from alterations of acid milieu of the stomach (e.g. by H2 receptor blockers or proton pump inhibitors). Consequently, for some products there are warnings included in the SmPC (e.g. Medikinet XL UK SmPC; section 4.5).

"Medikinet XL must not be taken together with H_2 receptor blockers or antacids, as this could lead to a faster release of the total amount of active substance."

We screened a number of SmPC of the prolonged release formulation of methylphenidate, and found that a warning regarding the possible effect of proton pump inhibitors on release of methylphenidate was missing in all of them.

We also found that a number SmPCs of other prolonged-release products did not carry any warning regarding H_2 receptor blockers, antacids, and proton pump inhibitors. However, some prolonged release products such as Concerta seem not to be affected might not be affected by changes of the gastric milieu.

The Rapporteur may therefore consider asking MAHs to check whether their products are affected by changes of the gastric milieu, and if applicable to submit a variation to update their SmPCs with a warning regarding "interaction" with H_2 receptor blockers, antacids, and proton pump inhibitors in section 4.5.

Lead Member State / PRAC assessment comment;

This interaction is not apparent from the PSURs submitted and reviewed to date. DE has observed that this interaction is not described in the SmPCs for all MPH products.

Stockley's Drug Interactions (May 2016) also notes:

"Theoretically, enteric-coated, delayed-release preparations may possibly dissolve prematurely if they are taken at the same time as antacids. This has been seen with some preparations, but not others. Release characteristics are likely to depend on the specific coating, and the manufacturer's advice should be followed."

Consequentially, there is a theoretical possibility that this interaction may be of importance to all of the longer-acting MPH products. Specific information concerning this interaction needs to be reviewed in

terms of formulation. It would be prudent for all MAHs to examine cumulative data of drug interaction between their longer acting formulations and H_2 receptor blockers, antacids or proton pump inhibitors.

MAHs of the longer-acting formulations should also present information on the release profiles of their formulations in terms of relative gastric acidity to ensure that the correct advice is provided in the SmPCs and Patient information.

Given the limited amount of time that the MAHs have to undertake this review prior to the next PRAC meeting, it is recommended that these reviews be presented within the next annual PSUR (DLP 31 October 2016), to facilitate an in depth, higher quality analysis of data. All sources should be explored, with follow up of cases containing minimal information in order to obtain missing information.

2. Signal and risk evaluation

2.1. Summary of safety concerns

The baseline summary of safety concerns for Ritalin products are:

Conclusion and actions	Risks / missing information	Risk status (new, ongoing, closed)**
There has been no change in the pattern of the risk; it will continue to be closely monitored.	**Important identified risks**	
	Hypertension*	Ongoing
	Tachycardia*	Ongoing
	Raynaud's phenomenon*	Ongoing
	Psychosis/mania*	Ongoing
	Hallucinations*	Ongoing
	Anorexia*	Ongoing
	Decreased rate of growth*	Ongoing
	Aggression*	Ongoing
	Depression*	Ongoing
	Important potential risks	
	QT prolongation*	Ongoing
	Arrhythmias*	Ongoing
	Ischemic cardiac events*	Ongoing
	Cyanosis*	Ongoing
	Sudden death*	Ongoing
	Cerebrovascular disorders*	Ongoing
	Hostility*	Ongoing
	Suicidality*	Ongoing
	Repetitive behaviors*	Ongoing
	Migraine*	Ongoing
	Tics/Tourette's syndrome/dystonias*	Ongoing
	Effect on final height*	Ongoing
	Sexual maturation (delayed)*	Ongoing
	Drug abuse and drug dependence*	Ongoing
	Withdrawal syndrome*	Ongoing

Conclusion and actions	Risks / missing information	Risk status (new, ongoing, closed)**
	Diversion*	Ongoing
	Off-label use*	Ongoing
	Carcinogenicity*	Ongoing
	Lymphocytic leukemia*	Ongoing
	Neonatal cardio-respiratory toxicity*	Ongoing
	Effects on neonatal growth*	Ongoing
	Cardiomyopathy*	Ongoing

Ritalin has EU RMP version 6.1 (dated 29 May 2015), which is applicable to both, pediatric and adult patients. It also has Core RMP version 2.0 (dated 02 Feb 2015)[18] which is applicable only to adult population. Hence, for the purpose of this PSUR, the risks will be presented in Sections 16.3 and 16.4 according to the EU-RMP classification.

The summary table of safety concerns for OROS-MPH duplicate those above; however differ for two safety concerns.

Ritalin includes the safety concern of cardiomyopathy which has not been added to the OROS-MPH table. OROS-MPH includes the identified risk of priapism.

Lead Member State/PRAC assessment comment: Cardiomyopathy was added as some Ritalin products are now authorised for use in adults and was requested by DE during the authorisation of adult use for Ritalin LA. Cardiomyopathy was reviewed in the article 31 referral, and considered to be a lower risk for children and adolescents. As the risk of cardiovascular disease can increase in the general population with age, this risk may be considered to be more important in this patient age group. This is accepted.

The identified risk of priapism is discussed further in section 2.3

2.2. Signal evaluation

Ritalin

Tabular overview of signals: there are no new validated signals identified during the reporting interval 1 November 2014 – 31 October 2015.

The following table presents risks not mentioned in the RMP but are presented in the PSUR:

Conclusion and actions	Risks / missing information	Risk status (new, ongoing, closed)*
All available data do not suggest a causal relationship with the Ritalin; the risk will be subjected to standard pharmacovigilance monitoring procedures	Priapism	Closed
There has been no change in the pattern of the safety concern; it will continue to be closely monitored.	Logorrhea	Ongoing
There has been no change in the pattern of the risk; it will continue to be closely monitored.	Bruxism	Ongoing
	Epistaxis	Ongoing
	Erection and penile disorders	Ongoing
	Erectile dysfunction	Ongoing
	Spontaneous abortion	Ongoing
	Congenital anomalies	Ongoing
	Spina bifida/neural tube defects	Ongoing
	Interaction with bupropion and erythromycin	Ongoing
	Interaction with risperidone	Ongoing
	Hyponatremia	Ongoing
	Aggression with overdose	Ongoing
	Pulmonary hypertension	Ongoing
	Valvulopathy	Ongoing

The MAH considers the ADR of priapism as not a validated signal. No validated signal was closed during the period 01 November 2014 to 30 October 2015.

Table 15-1 Health authority request from previous PSURs not categorized as validated signals, but required for continued monitoring

Topic	PSUR in which the request was made	Requester	Evaluation and summary of analysis
Priapism	Sandoz PSUR HP2[10]	The Medicines and Healthcare Products Regulatory Agency (MHRA)	- ICSR analysis - Literature review - Review of clinical trial data - Epidemiology review
Logorrhea	PSUR 11	MHRA	- ICSR analysis - Literature review - Review of clinical trial data - Epidemiology review

OROS-MPH

During the reporting period, the following signal has been closed with no safety issues:

- Rhabdomyolysis
- Enuresis
- Syncope and Loss of Consciousness

Medikinet

Signal term	Date detected*	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Actions taken or planned
Pancreatitis	10/2014	Closed	10/2014	(1)	Inconsistence with RSI	Review of individual case, internal database as well as scientific literature (MEDLINE)	No further action
Imaging procedure (Interference with DaTscan)	10/2014	Closed	10/2014	(10)	Inconsistence with RSI	Review of individual case as well as scientific literature (MEDLINE)	No further action
Overdose (with fatal outcome)	10/2014	Closed	10/2014	(8)	Inconsistence with RSI	Review of individual case, internal database as well as scientific literature (MEDLINE)	No further action

1. Artul S, Artoul F, Habib G, Nseir W, Bisharat B, Nijim Y. Severe recurrent pancreatitis in a child with ADHD after starting treatment with methylphenidate (Ritalin). Case Rep Gastrointest Med 2014;2014:319162.
8. Cantrell FL, Ogera P, Mallett P, McIntyre IM. Fatal oral methylphenidate intoxication with post-mortem concentrations. J Forensic Sci 2014 May;59(3):847-9.
10. Cheng G, Morley JF. Complete and readily reversible blocking of striatal DaTscan binding by methylphenidate. Clin Nucl Med 2014 Feb;39(2):211-3.

Lead Member State/PRAC assessment comment; the SmPC for OROS-MPH was updated with the ADR for Bruxism by variation and is not considered an important concern. Logorrhea is included in the SmPC for Ritalin and OROS-MPH and is not considered an important concern. Erection and penile disorders plus erectile dysfunction are ongoing concerns. Erectile dysfunction is included within the SmPC in section 4.8 of all MPH products. Both concerns are monitored in terms of priapism (discussed below in section 2.3). Rhabdomyolysis was added to the US product insert in April 2015. Janssen refuted this event however has been added as requested to the USPI as a consequence of 'overdose'. No further information is provided in the PSURs covering the period between 2013 -2015 from Janssen Cilag or Novartis concerning this serious event. However, Shire presented a cumulative review of case reports concerning Equasym / Medadate / Quasym which only identified one report which was

confounded by concomitant use of bupropion. This review was requested by the FDA from Shire's licence partner UCB Inc. It is unclear from the PSURs presented by Novartis and Janssen Cilag, whether this finding is similar for Ritalin and OROS-MPH. Cumulatively, Novartis identified a total of 14 reports (serious and non-serious) taken from spontaneous reporting and literature. Cumulatively 3 reports were identified by Janssen Cilag. However neither of these MAHs provided a detailed analysis of case reports. Therefore further information should be submitted concerning this serious event by Novartis and Janssen Cilag in the next PSUR.

Three reports of hyponatremia were identified for Ritalin during the period 2014 – 2015. Between 2012 – 2013 no additional reports were identified. Therefore evidence to support this signal is sparse. It is agreed that this signal should be ongoing.

The signals identified by Medice in the period 2013 -2014 were each derived from single literature reports. In terms of overdose with fatal outcome, this is not an unexpected outcome resulting from overdose. Fatalities are routinely reported in terms of individual adverse reports. During this period, there has not been a significant increase in the number of fatalities reported per year. Therefore, the conclusion of Medice is endorsed as these events are subject to routine pharmacovigilance.

2.3. Evaluation of risks and new information

OROS-MPH

During this reporting period, the following signal has been closed and is categorised as important identified risk: Drug Induced Liver Injury.

Priapism

Ritalin

Priapism is not listed in the Ritalin CDS or considered an important safety concern.

A search using MedDRA (version 18.1) was used to retrieve the relevant cases in the Novartis Global Safety Database. The search terms included the PT "Priapism". Cumulatively, there were 19 cases (including two incomplete cases) of Ritalin retrieved. Of the 17 valid cases retrieved for Ritalin, five were literature reports and twelve were SRs. Of these 17, three were non-HCP and 14 were HCP reports. Of these 17 cases, eight were classified as serious cases and the remaining nine were classified as non serious cases. Of the 17 cases retrieved for Ritalin, nine cases contained limited information and five cases had alternative explanations. In one case the patient experienced priapism three days after initiating therapy, although positive de-challenge was reported, there was limited information for a complete assessment of the case. In two cases priapism was reported as a withdrawal symptom after scheduled discontinuation of Ritalin with no recurrence of priapism with the sustained release formulation.

The RR comparison for the previous PSUR, reporting interval and cumulative period is mentioned in the table below:

Reporting rate comparison for "Priapism"

Drug	PSUR 13	PSUR 14	Cumulative
Ritalin	3.23	1.56	1.95

The RR in the reporting period 2014 – 2015 (PSUR14) is slightly lower than that of the previous reporting period 2013 - 2014 (PSUR 13) and the cumulative RR.

Eland IA et al in a study reported an overall incidence rate is 1.5 per 100,000 person-years (95% confidence interval 0.2 to 2.8) in general population. (Eland IA et al 2001. Incidence of priapism in the general population. Urology 57; 970-2)

Priapism results from alpha-1-adrenergic blockade in the corpora cavernosa leading to a parasympathetic-mediated arteriodilation as well as inhibition of the sympathetic system that leads to detumescence. This leads to an intracavernosal stasis owing to inadequate venous outflow caused by the obstruction of subtunical venules, resulting in hypoxia, acidosis and pain. Alpha-2-blockade exacerbates the alpha-1-mediated priapism by stimulating the release of a nitric oxide-like substance, which is a potent muscle relaxant. The nitric oxide-like substance is released from the neurons innervating the afferent arterioles and corpora cavernosa and this stimulates erections.

Methylphenidate is a sympathomimetic and psychostimulant drug and inhibits the presynaptic reuptake of catecholamines. It shows its central effect through dopamine rather than norepinephrine. However, vascular effects of the drug occur via the noradrenergic pathway through the sympathetic system. Because vascular smooth muscle relaxation is necessary for penile tumescence, these mechanisms are in apparent contradiction to the association of sympathomimetic like methylphenidate with priapism.

The MAH Shire undertook a similar review, presented in the PSUR covering the period 2013 – 2014. The Shire Global Safety systems (SGSS) database were searched using MedDRA version 16 for PTs contained within the HLT; Erection and Ejaculation Conditions and disorders, received cumulatively through to 30 September 2013 specifically for the trade names of Equasym/Metadate/Quasym (MH) and other trade names for MPH presented separately. Six spontaneous reports were identified, 5 of which identified erectile dysfunction in which none were suggestive of priapism or prolonged/increased erections, hence were excluded. The remaining case was non-serious describing a spontaneous erection in a 6 year old concomitantly treated with MH and clonidine. The report is lacking in information concerning ethnicity, medical history, drug allergy or whether there was any further additional concomitant medication. Treatment commenced with 20mg MH at unknown frequency in November 2010. Concomitant therapy with clonidine was indicated although no further information was provided. The time to onset of penile erection was not provided, however treatment with clonidine was reduced and the event resolved while MH therapy continued. Therefore this is a positive de-challenge for clonidine as opposed to MH.

Fourteen clinical trials were searched for reports of prolonged erections/ increased erections and priapism. No reports were identified.

Literature databases Medline and Embase were searched for all reports /articles relating to the use of MPH and/or MH and Ejaculation disorder, Erectile dysfunction, Erection increased, Nocturnal emission, Organic erectile dysfunction, Painful erection, Priapism, Psychogenic erectile dysfunction, Spontaneous ejaculation and Spontaneous penile erection. Seven case reports were identified of priapism/frequent prolonged erections occurring in association with MH. One article described 2 patients, while 2 articles identified the same patient.

- 3 reports describe a total of 2 patients receiving extended-release MPH who experienced “stuttering” priapism temporally-associated with MPH-free “drug holiday” periods (Schwartz and Rushton 2004; Ginsberg et al. 2004; Canadian Adverse Reaction Newsletter 2006).
- 1 report describes 2 patients receiving extended-release MPH who experienced sexual side effects, including frequent erections, only on days when they were exposed to MPH (Coskun and Zoroglu 2009);
- 1 report describes a patient receiving extended-release MPH, with scheduled weekly drug holidays, who reportedly experienced “short-lived’ erections daily for 2 years (Kelly et al. 2013);

• 1 report describes a patient on immediate-release (IR) MPH who presented with symptoms of intermittent priapism (Cakin-Memik et al. 2010); and
• 1 report describes a patient who experienced priapism while receiving concurrent therapy with MPH (formulation unspecified) and olanzapine (Husár and Zerhau 2006).

Seven of these reports involved longer acting MPH formulations and one instant release MPH.

Shire considered the inconsistency with regard to how priapism is defined, either as persistent erection not related to sexual behaviour of 4 – 6 hours, and the alternative as reaction that persists beyond or is unrelated to sexual stimulation. Two forms of priapism are also described as ischaemic or veno-occulsive (low-flow) and non-ischaemic (high-flow). Low-flow is the most common form leading to painful erections lasting beyond 4 hours characterised by absent cavernous blood flow. High flow is caused by unregulated blood flow and is characterised as an erection usually painless and not fully rigid. 'Stuttering priapism is described as "recurrent, self-limiting prolonged erections" and requires careful counselling as opposed to emergency treatment associated with low-flow priapism.

MPH causes the release of dopamine which has been proposed as a mechanism of action by which MPH can facilitate erection. Kelly et al (2013), noting that "sublingual dopamine agonists have been used as a treatment for erectile dysfunction, and hypersexuality is a recognised side effect of subcutaneous dopamine therapy in Parkinson's disease," considers it "probable that our patient's erections are mediated via the dopaminergic system". This is also recognised in several articles noting that dopamine antagonists such as anti-parkinsonian drugs may increase sexual libido and penile erection. Hence there is a plausible mechanism of action.

Shire concludes that there is sufficient information obtained from literature that there is sufficient evidence to support that prolonged or increased erections be added as ADRs to the Shire CCSI for MH. However there is insufficient evidence to support a causal relationship between MH and priapism.

OROS-MPH

Priapism is considered an important identified risk in the RMP (v5.0 dated 22/04/2014). The CDS contains the following warning;

"*Priapism: Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, including Methylphenidate HCl Extended-Release Tablets, in both paediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention*."

However, a warning concerning priapism or the adverse event of priapism is not included in the SmPC.

During the period 2014 to 2015, a total of 13 cases were received. These are summarised in the following table;

Table 38: Count of Selected MedDRA PTs by Age Consistent With Priapism or Increased Libido and Libido Disorder Reported With OROS® Methylphenidate Hydrochloride (n=12)

MedDRA PT	Number of Events		
Age (Years)	<18[a]	≥18[b]	NR[c]
Priapism	5	0	0
Erectile dysfunction	1	2	0
Delayed puberty	1	0	0
Libido decreased	0	1	0
Precocious puberty	1	0	0
Spontaneous ejaculation	1	0	0
Subtotal	**9**	**3**	**0**
Total	**12**		

Key: MedDRA= Medical Dictionary for Regulatory Activities; n= Number; NR= Not Reported; OROS= Osmotic Controlled-Release Oral Delivery System; PT= Preferred Term.

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

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

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

Lead Member State/PRAC assessment comment: The signal of Priapism has been under review through successive PSURs. The risk status is considered ongoing.

Not all case reports identified from the Novartis database have been described although 8 are considered to be serious with at least one positive de-challenge. Following the assessment of PSUR11 covering the period 2011 – 2012, it was noted that the number of reports of priapism are low but continue to be reported in subsequent years. It is also recognised that this event is a painful and debilitating event, with potential serious sequalae. The FDA published a MedAlert regarding the adverse event of priapism in patients treated with MPH, which has been followed by updates to reference safety information available in Northern and Southern America, Hong Kong and China. The FDA issued the warning on the basis of 15 case reports.

Within PSUR 13 covering the period 2013 – 2014 a further literature report was described;

Eiland LS et al (2014) Priapism associated with the use of stimulant medications and atomoxetine for attention-deficit/hyperactivity disorder in children. Ann Pharmacother 48; 1350-5. This paper reviewed literature obtainable from PubMed between 1966 to May 2014. Further information was taken from internet sources including the FDA website. This paper concluded that priapism is associated with all stimulants and atomoxetine used in the treatment of ADHD in children, however, this paper has inferred that this event is more often associated with the 'longer-acting' products, although has reported one case involving an instant release MPH.

The DHCP issued by Public Health Canada, only referred to 2 cases however implicated all MPH products including OROS-MPH and was endorsed by the MAHs for both Ritalin and OROS-MPH.

The mechanism presented by the MAH for Ritalin, by which priapism is induced or maintained is not clear. The argument presented relating to the release of an' nitric-oxide like substance' is theoretical. Similarly, the potential initiation of priapism by MPH is not apparent. The mechanism presented by Shire considering the MPH effect on dopamine receptor function is theoretically viable.

Priapism has been recognised in the CDS and RMP for OROS-MPH. The warning included in the CDS provides for a clear description of the reported events which have also been highlighted in the PSUR for the Ritalin products. This warning was recommended for inclusion by the FDA into all MPH products. Three further cases were identified in the period 2014 – 2015 for Ritalin although were either incomplete or not assessable due to lack of information. An additional 5 cases of priapism were identified in the period 2014 - 2015 for OROS-MPH within an overall identification of reactions of erectile dysfunction. Erectile dysfunction is included in the SmPC section 4.8 under the SOC Reproductive system and breast disorders. Priapism is an example of erectile dysfunction however, given the severity of this reaction, further information should be provided to investigate whether priapism has a significant association with erectile dysfunction.

It is noted that the safety concern of Priapism is included in the EU RMP v5.0 dated 22 April 2014 for OROS-MPH as an identified risk (procedure reference not provided). It is apparent that a greater number of cases may be identified for OROS-MPH products; therefore it is possible that there is a greater risk of onset for this product. However, no further information has been provided to describe the age of the patient or the circumstances of the event.

Medice states that 2 reports of priapism were identified, but for other MPH-containing products. There will be some duplication of numbers when data is extracted for the active MPH and not the trade name. Likewise, if data is only extracted by trade name, data will be missed. However, taken together there are a sufficient number of reports for which further information should be provided in order to assess any association with MPH. The inconsistency in the diagnosis of priapism is also of relevance in the identification of potential case reports. Therefore further information and cumulative review of all cases of prolonged or increased erections inclusive with priapism, be provided in the next PSUR. It is important for those MAHs who hold MAs for both the 'longer-acting' and the instant release formulations, to differentiate their review in terms of formulations.

NL comments:

We agree with the LMS that the signal of priapism in relation to MPH needs to be further investigated and that the further cumulative analyses should be requested from all MAHs. We would like to add that it would be most helpful if the cumulative analyses provided by the MAHs took into account (in addition to age already proposed by the LMS) the following factors: latency, the underlying conditions, concomitant medications, IR- or SR- formulation, if the event occurred in the treatment period or in the period the patient did not take MPH (e.g. drug holidays, drug discontinuation), the dosage and the reported positive de- and re-challenges.
Further, considering that priapism is a medical emergency and some of the published case reports indicate a possible relationship between priapism and methylphenidate, we suggest that this additional cumulative analysis is provided by the MAHs in response to this PAR.

Lead Member State / PRAC assessment comment:
Priapism has been under review through successive PSURs, and as yet, the information provided by the MAHs in terms of the cases reporting priapism, has not been acceptable. There is a distinct lack of information provided to enable a meaningful assessment. We agree that the maximum amount of information should be attained and provided for assessment, although we also need to consider that spontaneous reports do not always provide all this data. Therefore any cumulative review must incorporate the maximum amount of information taken from all available sources, including (but not exclusively) literature and clinical studies.

Throughout the assessment of these PSURs, it is becoming apparent that there are different safety profiles emerging from the use of the different formulations. This is an additional factor that needs to be taken into account in the overall analyses.

DE comments:

On page 40, the Rapporteur writes regarding priapism:
"… However, taken together there are a sufficient number of reports for which further information should be provided in order to assess any association with MPH. therefore further information and cumulative review should be provided in the next PSUR."

However, this recommendation is missing in section 3 "preliminary recommendations".

Apart from this, priapism has been under review through successive PSURs. After a first glance on the available literature, we believe that there is already very strong evidence for causal association. Several cases of priapism with compatible timelines, positive dechallenge, and positive rechallenge with MPH-containing products are described in the article of Eiland et al, 2014:
Example:
Schwartz described the case of a 15-year old boy with ADHD who experienced stuttering priapism associated with temporary withdrawal from a sustained release methylphenidate dosage form (OROS [osmotic controlled-release oral delivery system], Concerta). Priapism initially occurred after a dose increase from 27 to 36 mg daily. Doses were administered Monday to Saturday, with no administration on Sundays. The participant was not receiving additional medications and denied the use of illicit substances. The first episodes of priapism occurred on the Sunday following this dose increase and included 5 to 10 occurrences, each lasting 10 to 60 minutes. These recurred for several Sundays and additionally midweek, but only in the morning just prior to apparent drug administration and absorption (i.e., ending 45-60 minutes after oral drug administration in the morning). During a 7-day spring break vacation, stuttering priapism continued for 5 days after the last dose of methylphenidate. As the participant complained of afternoon fatigue, without revealing these episodes of priapism, his methylphenidate dose was increased to 54 mg daily. With this dose increase, the episodes of stuttering priapism increased in duration and intensity. When the participant admitted to this adverse effect, methylphenidate was discontinued. Other stimulants were not begun, and no further episodes of stuttering priapism occurred.

The MAH of Ritalin argues that because vascular smooth muscle relaxation is necessary for penile tumescence, these mechanisms are in apparent contradiction to the association of sympathomimetic like methylphenidate with priapism.
However, the described cases provide evidence that priapism is related to periods of drug withdrawal, and therefore are not in contradiction to what the MAH proposes.

See also FDA label:

"Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, including CONCERTA, in both pediatric and adult patients [see Adverse Reactions (6.6)]. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention."

Priapism is also an important identified risk for OROS-MPH as per summary of safety concerns.
However, to our knowledge priapism is not yet labelled in the SmPC of Concerta (dated July 2015).

In our view, the Rapporteur should consider to ask the MAHs for an update of the SmPC with this AE as an outcome of this PSUSA procedure – especially for OROS-MPH products.

Lead Member State / PRAC assessment comment:
We would like to thank DE for identifying the omission in section 3 of the preliminary AR. This has now been amended.

We endorse DE in their comment regarding the regular review of priapism. As a serious condition, it is important that this is kept under regular review. The article of Eiland et al 2014 is a review of all stimulants, concluding that all stimulants are associated with priapism.

The single case described by Schwartz involves a 15 year old male who was prescribed OROS-MPH. The patient experienced multiple episodes of priapism, which appear to have increased in frequency with an increase in dosage. The events also occurred midweek, apparently at a time when systemic levels would have been lower than usual. This has led to the hypothesis that the event of priapism is linked to withdrawal. However, this is a single case and at this time we do not have sufficient information to determine whether this is a valid hypothesis. The FDA label is only able to identify that events of priapism have been reported as there is a lack of information to either support or rule out this hypothesis.

Certainly, there are a greater number of reports of priapism originating from patients who are being treated with OROS-MPH, although we need to clarify if this event is associated with all 'longer-acting' MPH formulations. The hypothesis that priapism primarily occurs during a period of withdrawal or when systemic levels are low, would equally apply to all formulations. Similarly, if the event is in relation to MPH induced dopamine action, this would also involve all formulations of MPH. Therefore it would be judicious to review all case reports prior to any recommendation to update SmPCs.

Given the limited amount of time that the MAHs have to undertake this review satisfactorily prior to the next PRAC meeting, it is recommended that these reviews be presented within the next PSUR (DLP 31 October 2016) to facilitate an in depth, higher quality analysis of data. All sources should be explored, and follow up of the cases containing minimal information in order to obtain missing information.

The RMPv5.0 for OROS-MPH includes Priapism as an identified risk. However it is not clear when RMP v5.0 was approved. Given that priapism is not contained within the Concerta SmPC, it is therefore not considered to be an identified risk, however evidence has been provided that Priapism is a distinct potential risk for patients treated with OROS-MPH. Priapism is an important safety concern which requires further and regular review, therefore we recommend that the event of priapism be included in RMPs for all MPH products as a potential risk.

Drug Induced Liver Injury (DILI)

OROS-MPH

Hepatic enzyme increased was listed as an adverse reaction. DILI was identified as a safety signal for OROS-MPH based on a case from Germany of liver transplantation where a possible case of drug-induced liver disease was not excluded. Additionally a published case from Spain with liver transplantation related to DILI was identified. These 2 cases triggered a further cumulative review and evaluation.

The global safety database was searched for medically confirmed cases received during this reporting period (2014 – 2015) which met the PSUR reporting criteria and coded to the following MedDRA SMQ: Cholestasis and jaundice of hepatic origin (Narrow); Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions (Narrow).

Cumulatively 57 cases reporting drug induced liver injury were identified. This includes 1 additional case (literature) since the cumulative review completed in June 2015. Upon review, this case concerned multiple unidentifiable patients and is not further discussed. The remaining 56 medically confirmed cases reported 64 events of liver injury in patients who received methylphenidate HCl. The distribution of the PTs of interest is presented in Table 40 for the 56 cases retrieved.

Table 40: Distribution of the MedDRA PTs of Interest for Cases of Drug Induced Liver Injury Reported With OROS® Methylphenidate Hydrochloride (n=56)

MedDRA PTs	Number of Events[a]
Jaundice	15
Hyperbilirubinaemia	7
Drug-induced liver injury	6
Hepatic steatosis	5
Ocular icterus	5
Acute hepatic failure	3
Hepatocellular injury	3
Liver disorder	3
Liver injury	2
Varices oesophageal	2
Cholestasis	1
Hepatic cirrhosis	1
Hepatic failure	1
Hepatic fibrosis	1
Hepatic necrosis	1
Hepatitis fulminant	1
Hepatobiliary disease	1
Hepatotoxicity	1
Jaundice cholestatic	1
Liver transplant	1
Non-alcoholic steatohepatitis	1
Portal hypertensive gastropathy	1
Reynold's syndrome	1
Total	**64**

Key: MedDRA= Medical Dictionary for Regulatory Activities; n= Number; OROS= Osmotic Controlled-Release Oral Delivery System; PTs= Preferred Terms.
a: A single case may report more than 1 MedDRA PT of interest.

Cases were reported from varying countries. The majority of the patients were male (39 of 56, 69.6%). Of the cases with a reported age (42 cases), the mean age was 17.9 years and the median age was 14 years; age range was 9 to 61 years.

Table 44: Categorisation by Type of Liver Injury in the Reported Cases With OROS® Methylphenidate Hydrochloride

Type of Liver Injury	Number of Cases
Hepatocellular	18
Cholestatic	17
Autoimmune hepatitis	6
Mixed	5
Other Liver Injury	**Number of Cases**
Genetic	3
Unspecified	7
Total	**56**

Key: OROS®= Osmotic Controlled-Release Oral Delivery System

Of the 30 cases where latency was reported, more than half (n=16) reported a latency of more than a year.

Table 46: Outcome of Liver Injury Event for Cases Reported With Methylphenidate Hydrochloride

Outcome	Number of Events[a]
Recovered/Resolved	12
Recovered/Resolved With Sequelae	1
Recovering/Resolving	3
Not Recovered/Not Resolved	10
Fatal	1
Not Reported	37
Total Events	**64**

a: One case may report more than 1 liver injury event.

1 case reported a plausible temporal relationship between drug exposure and the AE, and 3 cases reported a positive rechallenge.

DILI is considered associated with the use of OROS MPH. Key factors supporting this conclusion include cases with a plausible latency, positive rechallenge, and cases with score 3 and above suggestive of possible causal relationship by applying CIOMS/RUCAM scale, causality assessment tool for hepatotoxicity.

MAH conclusion: The RSI was updated with the inclusion of the ADR hepatocellular injury and acute hepatic failure

Lead Member State/PRAC assessment comment; DILI may be the result of prolonged exposure. The latency of these reports would support this assumption. The conclusion given by Janssen is supported.by a plausible temporal relationship, 3 positive rechallenges, and 1 fatality.

The DUS identified that in some countries, the duration of treatment with MPH is increasing. The DUS took into account drug holidays of 8 weeks but this does not occur in all cases. Certainly diagnoses will be reviewed regularly, although the increased strain and effect on the parents or carers during drug holidays can be profound. Hence durations of continued treatment may be prolonged.

In the SOC Hepatobiliary disorders, a greater number of spontaneous reports (134) were received for Ritalin products. The majority of which are in relation to hepatitis related PTs and jaundice (26 reports).

The case reports retrieved for OROS-MPH, were equally divided between categorisations of hepatocellular and cholestastic injury, although a large number of events were reported for jaundice and hyperbilirubinaemia.

The SmPC includes hepatic coma and raised hepatic enzymes. Raised hepatic enzymes can be the result of multiple factors and indicative of hepatic injury. These case reports do not associate DILI with overdose. The MAH has decided to update their RSI with acute hepatic failure and hepatocellular injury as a very rare event. These are likely added in the context of the SMQ that was used to identify these cases, and therefore will include a wider collection of PTs which may be considered more acceptable given that in some cases DILI was not directly identified, although hepatocellular injury more often described. Further information is therefore required on these case reports and the ADR of DILI should be reviewed for all MPH medicines by all MAHs in successive PSURs as an ongoing signal, and a cumulative review provided in the next submitted PSUR.

FR comments:

The LMS AR is endorsed specially for the need to further characterize the DILI (drug induced liver injury) adverse drug reaction, to further assess the risk of cardiomyopathy and to provide an updated cumulative review of priapism cases.
Taking into account the 2 serious cases of hepatic disorders leading to a liver transplantation assessed in variation II77 for Concerta, the MAHs should further analyse cases leading to liver transplantation as part of the cumulative review. MAHs should consider whether there is a need for an update of section 4.4 of the SmPC.

2.4. Characterisation of risks

For all risks presented in the summary of safety concerns, a common set of analyses were undertaken. The information on the risks included in the summary tables for MPH and OROS-MPH remain unchanged.

Following a review of all case reports including serious and non-serious events and clinical studies, revealed that there was no important new safety information on the important risks or the topics with important missing information. All reports relate to events identified and reported in the reporting period.

Lead Member State/PRAC assessment comment: The safety concerns in relation to baseline safety concerns listed in section 2.1 above are unchanged. However for the period between 2014 and 2015; four reports of cardiomyopathy were identified and included within the PSUR for Ritalin. One of these cases did not involve abuse or drug dependence, and all were in adults. Cardiomyopathy was added to the Ritalin RMP as a potential risk following the variation to include an adult indication. In PSUR 13 (2013-2014), a cumulative analysis identified 26 cases. 10 cases were in patients <18 years of age, 8 of which were serious. Eleven cases were in patients >18 years. Out of the 26 cases, 3 were fatal with an age <18 years. The inclusion of cardiomyopathy in the Ritalin RMP is therefore a requisite for MPH used in patients with ADHD of any age.

Whilst the data has not been presented similarly in the PSURs for OROS-MPH, these important safety concerns continue to be reported across all ages. Whilst cardiomyopathy has not been specifically identified in the period 2014 - 2015, a number of fatalities occurred as the result of a serious coronary event. The MAH for OROS-MPH should submit a cumulative review of case reports of cardiomyopathy.

FR comments

1/ Pulmonary hypertension and valvulopathy

In the Ritalin PSUR, pulmonary hypertension and valvulopathy are considered as ongoing signals with methylphenidate. Cases reported during the PSUR period are not discussed by the LMS. However 2 cases of interest have been reported in France since 2014.
The first case is a case of mitral insufficiency reported in [redacted] treated with methylphenidate since September 2012. Medical history mentioned no cardiovascular risk. Concomitant treatments were cyproterone and estradiol. Cardiovascular standard check-up was normal at baseline, in 2013 and 2014. In April 2015, the patient presented mitral valve thickening with mitral leak. Methylphenidate treatment is stopped in April 2015.

The second case was reported [redacted] treated with methylphenidate for 2 years when [redacted] presented dyspnoea and restrictive cardiomyopathy. No cardiovascular medical history was reported. [redacted] was treated with dexfenfluramine during few months 20 years before dyspnoea beginning. Treatment with methylphenidate started in 2009. [redacted] 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.

Only PSURs for Ritaline and Quazym mentioned these risks. The MAH for Ritalin discussed the 5 cases of valvulopathy and the case of pulmonary hypertension reported during the PSUR period. The MAH concluded that the data received during the reporting interval did not reveal any new safety concern pertaining to 'valvulopathy' or "pulmonary hypertension". According to the MAH for Quazym, no case of valvulopathy or pulmonary hypertension has been reported during the PSUR period. The MAH did not mention these risks in the Concerta PSUR.

FR requests that all MAHs consider pulmonary hypertension and valvulopathy as ongoing signals which should be closely monitored in PSUR. New information including reported cases and published data need to be clearly identified and discussed in the PSUR section "signal evaluation".

Lead Member State/PRAC assessment comment*;* pulmonary hypertension and valvulopathy are regularly reviewed in PSURs. Therefore the LMS is satisfied that these adverse reactions are adequately reviewed by MAH.

2/ Congenital anomalies and spina bifida / neural tube defects

The risk of exposure during pregnancy has been assessed in 2008/2009 as part of the article 31 procedure. Safety Working Party advice was requested on the strength of the evidence on: the teratogenicity, foetal, neonatal and juvenile toxicity of methylphenidate; appropriate labelling for Core SPC sections 4.3, 4.6 and 5.3; need for further data or studies on the risks of use in pregnancy, lactation and in offspring/juveniles. SWP recommended that the contraindication for use during pregnancy be removed, and the Core SmPC wording be updated in line with the "Data To Labelling" Guideline. Because of the few weak cases of spina bifida/neural tube defect in humans and one rabbit study which showed cases in treated subjects at a maternally toxic dose of 200 mg/kg (equivalent to an HED of 64.5 mg/kg), but not higher than controls, the SWP recommended following up to obtain further information, if any, from EUROCAT, but that the proposed SmPC wording should be implemented without delay.

There were 5 cases of congenital anomalies with maternal exposure to methylphenidate in the EUROCAT database, for the years 1995-2010. To our knowledge, no further information on these 5 cases were provided by EUROCAT.

During the PSUR period, a publication about the teratogenicity of methylphenidate in mice was made available (Araujo Costa, 2016. Investigation of possible teratogenic effects in the offspring of mice exposed to methylphenidate during pregnancy, Reproductive Biomedecine Online 32, 170-177).
Pregnant Swiss mice were treated with MPH (5 mg/kg, subcutaneously) or 0.9% saline (control group) from the 5th to the 17th day of pregnancy. For the prenatal study, 30 pregnant females were used, whereas for the postnatal study, 24 were used. In the MPH-treated group, a significant increase in the total number of resorptions with a consequent increase in post-implantation loss and a decrease in fetal viability were detected. A total of 91.43% of resorptions were classified as early resorptions.
The group treated with MPH presented polydactyly, an external malformation (14.5% of foetuses affected vs 0.7% in control group).

Furthermore, an increased proportion of fetuses presenting incomplete ossification of the supraoccipital bone (68.7% vs 24.3%) and dilation of the brain ventricles (14.1% vs 2.8%) was observed. However, in the postnatal study, no behavioural alterations were detected.

Although this study has some limitations (only one dose group, SC dosing, no exposure measurement), it shows that methylphenidate induced malformations at a non maternotoxic dose equivalent to an SC dose of 0.4 mg/kg in human (based on Human Equivalent Dose [HED]).

Exposition during pregnancy should be closely monitored especially due to the extension of indication in the treatment of ADHD in adults available in some European countries. To date, the SmPC section 4.6 mentions that "Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses". Section 5.3 mentions that "Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses."

The MAH for Ritalin identified congenital anomalies and spina bifida / neural tube defects as ongoing signals. No case of spina bifida and one case of congenital anomalies (single umbilical artery) are reported during the PSUR period. The MAH mentions that there is no change in the pattern of these risks and these risks will continue to be closely monitored. However, the non clinical study in mice has not been identified and discussed. Also cases of congenital anomalies reported during the PSUR period are not presented by MAHs and not discussed by the LMS.

FR requests that all MAHs consider congenital anomalies and spina bifida / neural tube defects as ongoing signals which should be closely monitored in the next PSUR. New information including reported cases and published studies need to be clearly identified and discussed in the PSUR section "signal evaluation".

Lead Member State/PRAC assessment comment; Congenital anomalies and spina bifida/neural tube defects are considered as ongoing signals and are regularly reviewed or are presented in relation to the signal or discussed in terms of experience during pregnancy or lactation. Therefore the LMS is satisfied that these adverse reactions are adequately reviewed by MAH.

3/ Interaction with SSRI

Following article 31 referral, all the SmPc for methylphenidate containing products mention the interaction with SSRI in section 4.5 :
"However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbitol, phenytoin, primodone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times)."
Cases of serotonin syndrome are reported during the PSUR period. Case reports of serotonin syndrome in patients treated with SSRI and methylphenidate are also published including one case during the PSUR period (Motoyasu I, et al. Serotonin syndrome induced by augmentation of SSRI with methylphenidate. Psychiatry Clin Neurosci 2008; Turkotlu S. Serotonin syndrome with sertraline and methylphenidate in an adolescent. Clin Neuropharmacol 2015).
Taking into account these data, serotonin syndrome due to an interaction between methylphenidate and SSRI could be mentioned in SmPC. **FR requests that all the MAHs provide a cumulative review of serotonin syndrome cases in the next PSUR. Following this review, a SmPC update will be discussed.**

Lead Member State/PRAC assessment comment: The SmPC contains a warning concerning a potential interaction with SSRIs. During the period 2014 – 2015, only 2 cases were reported from Spontaneous reports/literature providing for a cumulative number of 11 reports for Ritalin products. Only 1 literature report was identified for OROS-MPH with a total of 3 case reports overall. Whilst it is acknowledged that serotonin syndrome is a serious adverse reaction, the SmPC provides a warning concerning this interaction. Therefore, a cumulative review is not considered necessary at this time.

4/ Article 31 referral outcome on harmonization

Safety concerns and signal (ongoing and closed) are not harmonized between each PSUR submitted as part of this procedure. It should be noted that one of the outcomes of the Article 31 referral procedure for all methylphenidate-containing medicinal products in the EU was that the Product Information of all methylphenidate-containing products should include the same safety information and the Risk Management Plans of these products should also be harmonized. A Core Risk Management Plan (RMP) was required for all products containing methylphenidate.

Although the PSUSA procedure is not a procedure for harmonization, the article 31 conclusions highlights the need for harmonization between all methylphenidate containing products. Hence, **FR proposes that ongoing signals and safety concerns be harmonized between each PSUR submitted as part of the PSUSA procedure. That will also facilitate the LMS assessment.**

Lead Member State/PRAC assessment comment: It is agreed that it would be helpful if all ongoing signals and safety concerns were harmonised between each PSUR. However, at this point it is apparent that there are differences between safety concerns between Ritalin (and associated MPH products), and OROS-MPH. These differences may be related to formulation, therefore it would be helpful for us to review and assess these differences between the formulations as requested from the MAHs, before a further recommendation on this proposal can be made.

5/ Important potential risk of the core RMP

"Hostility", "cyanosis", "tics" and "drug abuse and dependence" have been identified as important potential risks in the core RMP. However, "tics", "drug abuse and dependence", "hostile behavior", "Raynaud's phenomenon" are mentioned as known adverse effects with methylphenidate in sections 4.4 and 4.8 of the SmPC.
FR consider that these risks should be removed from the important potential risks and the need to mentioned these risks as important identified risks or to remove these risks from the RMP from should be discussed.

Lead Member State/PRAC assessment comment ; It is proposed that a discussion of the summary table of safety concerns in the RMP in terms of the relative positioning for the concerns as either an identified or potential risk should be undertaken during the next type II variation procedure involving an RMP update.

3. Benefit evaluation

Ritalin has been used for over 50 years in the treatment of ADHD. Its effectiveness in the treatment of ADHD is well established. MPH has been shown to be efficacious in children and adults.

The place of OROS-MPH in the treatment of ADHD is well established. OROS-MPH has additionally been authorised for use in children, adolescents, and adults (up to 65 years of age) with ADHD in a number of countries since 2008, although not in Europe. During the period 2014-2015, efficacy from eight clinical studies, 6 in patients <18 years and 2 in adult patients, results were shown to be consistent with the known efficacy of OROS-MPH. However, one withdrawal clinical trial in adults showed little difference between placebo and OROS-MPH. This has been described as being due to issues regarding the study design. OROS-MPH is not authorised for use in adults with ADHD not previously identified from childhood. This does not provide compelling information to support efficacy of OROS-MPH in this patient population, within Europe. However, detailed analyses of studies presented as supportive of efficacy cannot be undertaken within this procedure.

DE comments:

1. New Cochrane Review
Shortly after DLP of this PSUR a Cochrane review was published assessing the study question: "*Is methylphenidate beneficial or harmful for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents?*"[2]
The study concluded:

[2] Storebø OJ, Krogh HB, Ramstad E, Moreira-Maia CR, Holmskov M, Skoog M, Nilausen TD, Magnusson FL, Zwi M, Gillies D, Rosendal S, Groth C, Rasmussen KB, Gauci D, Kirubakaran R, Forsbøl B, Simonsen E, Gluud C. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. BMJ. 2015 Nov 25;351:h5203.

Methylphenidate use in children and adolescents may improve the symptoms of ADHD, general behaviour, and quality of life. It does not seem to cause an increased risk of serious adverse events in the short term but was associated with a relatively high risk of non-serious adverse events. These findings should be interpreted in the light of several limitations, including the lack of blinding, outcome reporting bias, heterogeneity, and the consequent very low quality of evidence for all outcomes. More long term randomised nocebo tablet (active placebo) controlled clinical trials without risks of bias are necessary to allow firm decisions on methylphenidate treatment in children and adolescents with ADHD. We believe that nocebo controlled trials should be conducted first in adults with ADHD.
Of note, the authors noted that 96.8% of trials were considered high risk of bias trials according to the Cochrane guidelines. All outcomes were assessed very low quality according to GRADE.

We propose that the MAHs are asked to discuss this Cochrane study in detail, and explicitly comment on the author´s conclusion that benefits are modest and reviewed trials have a high risk of bias.

Lead Member State / PRAC assessment comment*:* A further review was published[3]. This latest publication indicates that there is stronger evidence that supports the use of longer-acting methylphenidate and amphetamine formulations, atomoxetine, and extended-release guanfacine to improve symptoms of ADHD in adolescents. These newer formulations have been subject to greater control with studies undertaken using updated and agreed guidelines. However, due to the historical birthdate, clinical studies examining efficacy in the older preparations of immediate release methylphenidate were undertaken with little guidance. Similarly, the efficacy of MPH was evaluated in the treatment of a newly identified medical diagnosis which itself was under evaluation as a specific psychosis. Both reviews impart relevant information and agree that treatment using MPH is beneficial to adolescents with ADHD. Both reviews also provide recommendations for further research.

In the light of these two latest publications, the comment of DE is endorsed, and the MAHs are requested to discuss these latest publications in the next PSUR (DLP 31 October 2016) in terms of benefit.

NL Comments:
Last year signals of drug-inefficacy after switching from Concerta to generic slow-release products have been discussed by the LMS (EPITT Reference 18522). The LMS could not confirm this signal. Since then more reports have been received in the NL. In view of these reports we received from our national reporting center Lareb we would appreciate if the UK could include a request to the MAH to review and discuss signals of drug-inefficacy after switching to generics.

[3] Eugenia Chan; Jason M. Fogler; Paul G. Hammerness. Treatment of Attention-Deficit/Hyperactivity Disorder in AdolescentsA Systematic Review *JAMA.* 2016;315(18):1997-2008.

Lead Member State / PRAC assessment comment: The majority of the MAHs for these trade named products, also have MAs for the same product but with a generic name. Therefore it will be difficult for either MAH to identify if there is an issue concerning efficacy as an outcome from a switch from their branded name product to their generic named product, i.e. Concerta to OROS methylphenidate. However it is possible that there may be issues concerning efficacy when switching between the different 'longer acting' MPH medicines owing to the different release profiles. These reports can be confounded by patient bias, however when taking into account the late breaking information reported by Medice, there is the theoretical possibility that release profiles may be affected by gastric milieu. Lack of efficacy is a safety concern that is monitored by each MAH and reported in each PSUR although needs to be discussed in greater detail. The MAHs need to identify all possible reasons why the patient experiences lack of efficacy when switching between the branded product and generics, or between generics. Details need to be provided as to the specific change in product, whether there is an association with formulation, a change between manufacturers, or drug-drug interaction. Details need to be provided as to when the lack of efficacy becomes apparent either to the patient themselves or the patient carer. Hence further details need to be given on the time to onset.

4. Benefit-risk balance

ADHD is a behavioural disorder expressed as inattention and distractibility with periods of 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.

Methylphenidate has been used and shown to be efficacious in the treatment of ADHD in children between the ages of 6 and 18 years, and adults. The larger population of patients diagnosed with ADHD continues to be within the ages of 6 – 18 years. However ADHD may not resolve in all cases prior to the patient reaching adulthood. DSM 5 provides greater guidance on the diagnosis ADHD in adults who have not previously been identified, if symptoms were exhibited during childhood. As a consequence, overall MPH is increasingly being prescribed throughout Europe within the adult population. However the exposure of OROS-MPH is decreasing in comparison with exposure to Ritalin. OROS-MPH was developed as a longer-acting MPH product, allowing for a single dose to be taken at the start of the day. Data obtained from the Ritalin PSURs does not differentiate between the instant release products and those of extended release, sustained release, or modified release ('longer acting' MPH) hence it is not possible to see if this pattern is reflected between the Ritalin products.

As expected the largest proportion of spontaneous reports originate from the SOCs psychiatric disorders and nervous system disorders. These are known to predominate in this patient population, and therefore are not unusual. Of interest, there are a greater cumulative number of spontaneous reports of self-injury presented in the PSUR for OROS-MPH compared with Ritalin. The use of MPH and OROS-MPH is contraindicated in patients with depression or suicidal tendencies. Whilst overall the numbers of self-injurious reports may be low, self-injury can have serious consequences. Given that there is a greater exposure of Ritalin compared with OROS-MPH, a further review is needed to determine if this is related to formulation.

For both Ritalin products and OROS-MPH, the highest frequency PT for medication error is "wrong techniques in drug usage process", for example the division of tablets or capsules, or the sprinkling of capsule contents onto food. This can be associated with a wider interpretation of events within individual case reports, such as non-compliance.

The recognised safety concerns remain valid. Both Ritalin and OROS-MPH have very similar safety concerns, although Ritalin includes the additional safety concern of cardiomyopathy. Conversely OROS-MPH includes an identified risk of priapism.

Cardiomyopathy was reviewed in the article 31 referral and considered that is was not an important safety concern owing to the rarity of the event in children. Cardiomyopathy was added to the Ritalin RMP as a potential risk following the variation to include an adult indication for Ritalin LA. Data supports the inclusion of cardiomyopathy as an important potential risk for Ritalin although it cannot be determined whether this relates to all MPH products, or to specific age groups.

The signal of Priapism has been under review through successive PSURs, as it is recognised that this event is a painful and debilitating event, with potential serious sequalae. Therefore, priapism is considered to be an important safety concern for all MPH products although is already recognised in the CDS and RMP for OROS-MPH. There is the possibility that the reported cases of priapism have a greater potential association with 'longer-acting' formulations. Similarly, there are implications concerning an association with withdrawal. However, there is a lack of information provided for meaningful assessment and therefore a cumulative review would provide for greater detail.

DILI was identified as a potential signal by the MAH for OROS-MPH. The MAH has therefore decided to update their RSI with acute hepatic failure and hepatocellular injury as very rare events. The case reports retrieved for OROS-MPH, were equally divided between categorisations of hepatocellular and cholestastic injury. A greater number of spontaneous reports for hepatobiliary disorders were received for Ritalin products, the majority of which are in relation to hepatitis related PTs and jaundice. Although a large number of events were reported for jaundice and hyperbilirubinaemia. Consequentially further characterisation of these spontaneous reports should be provided and a review of all cases of DILI provided in the next PSUR by all MAHs.

The signal of Rhabdomyolysis was added to the US product insert in April 2015. However little information has been provided on this serious concern in the PSURs covered by this PSUSA therefore a cumulative review of rhabdomyolysis is requested for the next PSUR.

Late-breaking information provided by Medice has identified an interaction between the longer acting MPH formulation, "Medikinet XL" and H_2 receptor blockers/proton pump inhibitors. Dependent upon the release profiles of these MPH products, it is theoretically possible that the pH of the gastric milieu would have an effect on the release of the active medicine MPH.

Whilst the harmonised and recognised safety concerns have not altered for all MPH medicines, new safety concerns have been identified by the MAHs that differ between OROS-MPH and Ritalin. OROS-MPH is a 'longer acting' formulation; therefore reports presented in the PSURs for this product are specific to this formulation. PSURs for Ritalin cover both instant release and 'longer acting' MPH formulations, therefore in order to determine if these new signals are related to formulation, presentations of reported and suspected ADRs according to formulation will aid future evaluation. Overall, based on the information received during the review period, it is concluded that the benefit-risk balance of MPH in the licensed indication for the treatment of ADHD remains unchanged.

5. Lead Member State Request for supplementary information

None

6. MAH(s) responses to preliminary recommendations for issues to be addressed in the next PSUR

Shire

- The MAHs are recommended to undertake a review of all cases of self-injurious behaviour.

Response:
This is already encompassed within the Shire PSUR template under Evaluation of Risks for Psychiatric and Neurological Disorders: Suicidality. Shire agrees to continue review of all cases of self-injurious behaviour.

- The ADR of DILI should be closely monitored for all MPH medicines in successive PSURs as an ongoing signal on a cumulative review provided in the next PSUR.

Response:
Shire will add review of all DILI case reports to the next PSUR

- The MAHs, Janssen Cilag and Novartis should provide a cumulative review of Rhabdomyolysis with the provision of more detailed information on the individual case reports and conclusion.

Response:
Shire will continue to review all case reports of Rhabdomyolysis within the Shire PSUR template under Evaluation of Risks for Musculoskeletal and connective tissue disorders.

- The signal of Priapism was highlighted in previous PSUR assessments and has been under review through successive PSURs. Priapism is a painful and debilitating event, with potential serious sequalae. Albeit in low numbers, serious case reports of priapism continue to be identified although case report information is limited. Therefore an updated cumulative review should be undertaken by all MAHs, and to consider if the event is age related.

Response:
This is already encompassed within the Shire PSUR template under Evaluation of Risks for Other Events under Investigation: Penile Disorders including Priapism. Shire agrees to continue review of all cases of Priapism.

- In future PSURs, analysis of safety in terms of MPH formulation should be presented in those PSURs where multiple formulations are included.

Response
Not Applicable for Shire.
The medication is approved in 18 countries worldwide for ADHD and marketed in 14 countries in one formulation of modified-release capsules 10, 20, 30, 40, 50 and 60 mg strengths.

Lead Member State/PRAC assessment comment: Shire has agreed to undertake the reviews of Priapism, Rhabdomyolysis, DILI, and self-injurious behaviour as requested in the preliminary AR. However, the recommendations are made in terms of cumulative review. Events of self-injurious behaviour are distinct from the reports concerning suicidality. Therefore the recommendations of review in the next PSUR have been amended in this updated Preliminary AR.