13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Attention Deficit Hyperactivity Disorder

Ritalin is used for the treatment of attention deficit hyperactivity disorder, also known as ADHD. ADHD is one of the most common childhood disorders and can continue throughout life. The average age of onset is 7 years old. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and over-activity. Around the world about 6-12% of children are estimated to be affected by ADHD. Approximately 40-80% of children diagnosed with ADHD continue to exhibit symptoms in adolescence. In the United States, about 16% of 19 year olds have a probable or confirmed diagnosis of ADHD. This is equivalent to 4 out of every 25 nineteen year olds. ADHD is three times more common in males than females.

Narcolepsy

Ritalin is also used for the treatment of a sleep disorder called narcolepsy. Narcolepsy is a sleep-attack disorder. People with narcolepsy experience periods of extreme daytime sleepiness and sudden, irresistible bouts of sleep that can strike at any time despite adequate night-time sleep. These "sleep attacks" usually last a few seconds to several minutes. Symptoms often start in childhood or adolescence, but can occur later in life. The condition is life-long. Narcolepsy is not rare, but it is an under recognized and underdiagnosed condition. Approximately 1 out of every 3500 people experience narcolepsy, and it is more commonly seen in males than females. Narcolepsy is most likely to start during second decade of an individual's lifespan. One out of three people who will have narcolepsy during their lifetime start experiencing it by the age of 15 years.

13.2.2 Part VI.2.2 Summary of treatment benefits

13.2.2.1 ADHD

Ritalin, Ritalin SR and Ritalin LA are intended for use in patients aged 6 years and older with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD).

In addition to improving core symptoms of ADHD, MPH also improves behaviors associated with ADHD such as impaired academic performance and social function.

Currently treatment of ADHD is based on a comprehensive program which includes psychological, educational and social measures as well as pharmacotherapy. The most frequently used pharmacotherapy currently is MPH.

The Ritalin LA formulation was demonstrated to be effective in pediatric ADHD in two adequate and well-controlled clinical studies in 195 children aged 6-12 years with ADHD in the original submission for marketing authorization of Ritalin LA.

The results of these studies proved a significant difference showing Ritalin LA to be effective compared to the pill with no active medication. The efficacy of Ritalin LA was consistently reflected in the assessments of teachers, parents and investigators.

Since the year 2000, Ritalin LA was consistently found to be effective and safe in the treatment of ADHD in patients aged 6 years and above over short term and long term studies in more than 800 children and 725 adults diagnosed with ADHD in multiple studies spanning across duration of 2 weeks to 66 weeks in comparison with Concerta, Medikinet and pill with no active medication.

The data observed in the pivotal adult study (RIT124D2302) is consistent with the efficacy and safety observed in the treatment of children with ADHD.

13.2.2.2 Narcolepsy

For narcolepsy, first line treatment is behavioral modifications, such as taking planned daytime naps and to avoid stressful events that may trigger attacks followed by drug therapy such as Ritalin (a MPH product) due to its rapid onset of action.

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Ritalin in the treatment of ADHD is well established for last 40 years. In addition to improving core symptoms of ADHD, MPH also improves behaviors associated with ADHD. Ritalin has also been shown to significantly improve daytime sleepiness and cataplexy in published literature.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-4 Important identified risks

Risk	What is known	Preventability
High blood pressure (Hypertension)	Approximately one out of five hundred people treated with Ritalin in clinical studies developed high blood pressure. This number is slightly higher for people treated with Focalin, at about six per five hundred people. The degree of high blood pressure varies from non-serious to serious. For patients taking Ritalin that reported developing high blood pressure, a little less than half of the cases were serious and about 15% of these patients were hospitalized. For patients taking Focalin that reported developing high blood pressure, a little more than half of the cases were serious and about 6% of these	Education of prescribers and patients/caregivers; early detection, monitoring and therapy including drug therapy, nutritional and lifestyle changes.

Risk	What is known	Preventability
	patients were hospitalized. For people who already have severe hypertension, Ritalin is not supposed to be used.	
Fast heart rate (Tachycardia)	Approximately two out of five hundred people treated with Ritalin will develop a fast heart rate. This number is higher in people treated with Focalin, at about fourteen per five hundred people treated. The seriousness of having a fast heart rate varies from not serious and the patient experiencing no symptoms or complications, to very serious and the patient experiencing a heart attack or even death. Of the patients taking Ritalin who reported experiencing an increased heart rate, 5 out of 11 cases were serious. Of the patients taking Focalin who reported experiencing an increased heart rate, 4 out of 11 cases were serious.	Education of patients, caregivers and prescribers. Early detection, monitoring and therapy including drug therapy (e.g. anti-arrhythmic drugs), nutritional (low-fat, controlled diet) and lifestyle changes (avoid stimulants such as caffeine, nicotine, some decongestants and illegal drugs).
Blocked blood flow to fingers or toes (Raynaud's phenomenon)	In studies, no patients taking Ritalin developed this, and only one out of over 1600 patients taking Focalin developed this. The severity of the blocked blood flow can vary from non-severe, where the patient is in no pain but their fingers or toes turn a bluish color, to more serious cases where people can experience pain and develop sores on their skin. Of the patients that reported developing this blocked blood flow after taking Ritalin when the drug was made available to the public, a little less than half were serious. Of the patients that reported developing this blocked blood flow after taking Focalin, a little more than half were serious. This blocked blood flow is worsened by being in a cold area or by strong emotions.	Protection from the cold.
Abnormal condition of the mind/ abnormal mood (Psychosis/mania)	Abnormal condition of the mind: Approximately three out of five hundred patients receiving Ritalin experienced this. With Focalin twenty-one per five hundred patients experienced this. The seriousness of this abnormal condition of the mind varies. Of the patients taking Ritalin that reported experiencing this, 47.5% of the cases were serious. For Focalin, 35% were serious. Abnormal Mood: About one out of five hundred patients taking Ritalin experienced this, and about twelve out of five hundred patients taking Focalin experienced this. Of the patients taking Ritalin that reported experiencing this, 90% of the cases were serious. For Focalin, 75% were serious.	Education of prescribers, patients and caregivers. Early detection and management of psychiatric
Visual image, sound or sensation with no external cause	In studies, no patients receiving Ritalin developed hallucinations. Approximately one out of 800 patients receiving Focalin developed	Education of prescribers, patients and caregivers. Early detection and

Risk	What is known	Preventability
arising from a brain disorder (Hallucinations)	hallucinations. Of the patients taking Ritalin that reported experiencing hallucinations, 72% of the cases were serious. For Focalin, 92% of the cases were serious.	management of symptoms.
Decreased appetite (Anorexia)	Approximately 50 out of 500 people treated with Ritalin will experience some form of decreased appetite. For Focalin, about 70 out of 500 people will experience this. The seriousness of the decrease in appetite varies from slight weight loss to fatalities. Of the patients taking Ritalin that reported experiencing a decreased appetite, 19% of the cases were serious. For Focalin, 11% of the cases were serious.	Education of prescribers, patients and caregivers. Early detection and management of symptoms (counseling, encouraging a healthy attitude to eating and weight).
Decreased rate of growth (Decreased rate of growth)*	It is difficult to assess the likelihood of experiencing a decreased rate of growth after taking Ritalin or Focalin, since there were no cases of this in any of the studies. The seriousness of the decreased rate of growth varies in reports received since the drug was made available to the public. Of the patients taking Ritalin that reported experiencing this, 40% of the cases were serious. For Focalin, 20% of the cases were serious.	Patients, caregivers and prescribers should be aware of the possible impact of long term use of Ritalin on growth.
Aggressive mood (Aggression)	Approximately 19 out of 500 people treated with Ritalin will experience some form of aggressive behavior. For Focalin, about 38 out of 500 will experience this. The seriousness of the aggression varies from aggressive comments to aggression related death. Of the patients taking Ritalin that reported experiencing this, about 40% of the cases were serious. Of the patients taking Focalin, about 27% of the cases were serious.	Education of caregivers, prescribers, early detection and management of symptoms and things that could increase the risk of developing aggression.
Depressed mood (Depression)	Approximately 21 out of 500 people treated with Ritalin will experience some form of depression. About 50 out of 500 people treated with Focalin will experience some form of depression. The severity of the depression varies from intermittent sadness to suicidal thoughts resulting in death. Of the patients taking Ritalin that reported experiencing depression or depressed mood, about 56% of the cases were serious. Of the patients taking Focalin, about 81% of the cases were serious.	Early detection, appropriate diagnosis and management including drug therapy and psychological therapy to prevent relapses; education of prescribers, patients and caregivers.

*Safety concern applicable specifically to children

Table 13-5 Important potential risks

Risk	What is known
Increased time between heart beats (QT prolongation)	Reports have been received of patients taking MPH that experienced increased time between heart beats but no strong link to the use of MPH has been observed.

Risk	What is known
Abnormal heart rate (Arrhythmias)	This is considered a potential risk because other medications in the same class have this risk. Reports have been received of patients taking MPH that experienced an abnormal heart rate.
Heart problems caused by decreased blood flow (Ischemic cardiac events)	There is a theoretical mechanism behind this that involves the possibility of the medication narrowing the blood vessels. Reports have been received of patients taking MPH that experienced heart problems caused by decreased blood flow.
Bluing of the skin due to decreased oxygen in the blood (Cyanosis)	There was a report in a medical journal that said MPH may induce abnormalities in blood vessels in the limbs and cyanosis. Reports have been received of patients taking MPH that experienced skin having a blue tinge due to decreased oxygen in the blood.
Sudden death usually caused by heart illness (Sudden death)	It is not known why but experts believe this could possibly be related to existing heart problems. Reports have been received of patients taking MPH that experienced sudden death.
Decreased blood flow to the brain (Cerebrovascular disorders)	This is considered a potential risk because other medications in the same class have this risk. Reports have been received of patients taking MPH that experienced decreased blood flow to the brain.
Angry behavior (Hostility)	Reports have been received of patients taking MPH that started to feel hostile.
Behaviors and actions that are directed to cause one's own death (Suicidality)	There are theoretical mechanisms behind this, but no cases were seen in Ritalin clinical studies, or the clinical studies of other medications in the same class. Thoughts or attempts of suicides have occurred in patients taking other medications in this class. Reports have been received of patients taking MPH that experienced suicidality.
Repetitive or ritualistic movement/ behavior, posture or speech (Repetitive behaviors)	This is considered a potential risk because other medications in the same class have this risk. Reports have been received of patients taking MPH that experienced repetitive behaviors.
Moderate to severe headaches typically affecting one half of the head associated with other symptoms such as nausea, vomiting sensitivity to sound, light or smell (Migraine)	There is a theoretical mechanism behind this, and other medications in the same class have this risk. Reports have been received of patients taking MPH that experienced migraines.
Repetitive, involuntary movements (Tics/Tourette's syndrome/dystonias)	There is a theoretical mechanism behind this potential risk, and it has been seen with other medications of the same class. Reports have been received of patients taking MPH that experienced repetitive, involuntary movements.
Effect on final height (Effect on final height)*	It is not known why this may occur but experts this could possibly be because methylphenidate-containing products decrease appetite, leading to changes in weight that could impact growth and final height. Also, other medications in the same class have this risk. Reports have been received of patients taking MPH that experienced an effect on final

Risk	What is known
	height.
Sexual maturation (delayed) [Sexual maturation (delayed)]*	There was an animal study that showed a delay in sexual maturation, however there was a similar animal study that did not show a delay in sexual maturation. There is no human data showing this delay in sexual maturation. Reports have been received of patients taking MPH that experienced delayed sexual maturation.
Drug abuse and drug dependence (Drug abuse and drug dependence)	Other medications in the same class have this risk. Reports have been received of patients taking methylphenidate that experienced drug abuse and drug dependence.
Symptoms after stopping the medication (Withdrawal syndrome)	Reports have been received of patients taking methylphenidate that experienced symptoms after stopping the medication.
Use of the medication for recreational purposes (Diversion)	There is a theoretical mechanism behind this that involves the abuse potential of the medication. Reports have been received of patients taking MPH that altered the prescription form
Using the medication for something other than what it was intended for (Off-label use)	Reports have been received of patients taking methylphenidate that used the medication for something other than what it was intended for.
Cancer (Carcinogenicity)	In animal studies new cancers were discovered, however, the animals were being given significantly higher doses than is recommended in humans. A study was conducted in humans to see if there was the same observation as in animals. In humans, no increased risk in developing new cancers was seen. Reports have been received of patients taking MPH that developed cancer, but no strong link to the use of methylphenidate has been observed.
Cancer in the blood stream (Lymphocytic leukemia)	Reports have been received of patients taking methylphenidate that developed cancer in the blood stream. But no strong link to the use of MPH has been observed.
Newborn heart or lung problems (Neonatal cardio-respiratory toxicity)	It is unknown whether exposure of the fetus to methylphenidate could have effects on the heart and lungs as medications in the same class are known to cause problems. Reports have been received regarding MPH and newborn heart or lung problems.
Newborn effect on growth (Effects on neonatal growth)	There have not been any cases of this, but it is known that Ritalin can cause a decreased rate of growth. It is unknown whether exposure to the fetus could have a similar effect. No reports of newborn effect on growth have been received.
Heart disease due to abnormality in the heart muscle (Cardiomyopathy)	Reports have been received of patients taking MPH that experience disorder of the heart muscle but no strong link to the use of MPH has been observed.

*Risks applicable specifically to children

Table 13-6 Missing information

Risk	What is known
None	Not applicable

13.3 Part VI.2.5 Summary of additional risk minimization measures by safety concern

These additional risk minimization measures are for the following risks:

- High blood pressure (Hypertension)
- Fast heart rate (Tachycardia)
- Abnormal condition of the mind/abnormal mood (Psychosis/mania)
- Visual image, sound or sensation with no external cause arising from a brain disorder (Hallucinations)
- Decreased appetite (Anorexia)
- Decreased rate of growth (Decreased rate of growth) – Risk specific to children
- Aggressive mood (Aggression)
- Depressed mood (Depression)
- Abnormal heart rate (Arrhythmias)
- Heart problems caused by decreased blood flow (Ischemic cardiac events)
- Sudden death usually caused by heart illness (Sudden death)
- Decreased blood flow to the brain (Cerebrovascular disorders)
- Angry behavior (Hostility)
- Behaviors and actions that are directed to cause one's own death (Suicidality)
- Repetitive, involuntary movements (Tics/Tourette's syndrome/dystonias)
- Drug abuse
- Drug Dependence
- Symptoms after stopping the medication (Withdrawal syndrome)
- Use of the medication for recreational purposes (Diversion)
- Using the medication for something other than what it was intended for (Off-label use)

Table 13-7 Additional risk minimization activity for safety concerns listed above

Risk minimization measure(s): A MPH information resource website which will provide access to the following educational materials: 1) Physician's guide to prescribing, and 2) Checklists for actions before prescribing and for ongoing monitoring for prescribers and, if possible, caregivers. These materials provide guidance on the safe use of MPH. The content of the website is available in the 23 official EU languages.
Objective and rationale
To educate physicians on the safe use of MPH. This is achieved by providing educational tools on a website to help physicians stay well-informed and use MPH according to the most recent safety information.
Proposed actions
This project is strictly for medical education purposes. It is not intended for promotion of products. To ensure this, the website was developed by an outside company. The key messages of this educational tool are as follows:

Risk minimization measure(s): A MPH information resource website which will provide access to the following educational materials: 1) Physician's guide to prescribing, and 2) Checklists for actions before prescribing and for ongoing monitoring for prescribers and, if possible, caregivers. These materials provide guidance on the safe use of MPH. The content of the website is available in the 23 official EU languages.
1) Providing information on diagnosis, medical history, and assessment of other concurrent disease a patient has. The website will guide physicians on what laboratory values need to be monitored, as well as providing a tool for documentation. The goal is to inform doctors on what information they need to collect from their patients to make sure only the appropriate patients are given the medication. 2) Monitoring during treatment related to safety aspects including blood pressure, heart rate, height and body weight, and occurrence or worsening of pre-existing psychiatric symptoms, tics, or seizures. Also, the educational tool will address recommended periods off medication.

13.4 VI.2.6 Planned post authorization development plan

13.4.1 List of studies in post authorization development plan

Not applicable

13.4.2 Studies which are a condition of the marketing authorization

None

13.5 VI.2.7 Summary of changes to the Risk Management Plan over time

Table 13-8 Major changes to the Risk Management Plan over time

RMP Version	RMP Date	Safety Concerns	Comment
3	15-Oct-2008	**Identified Risks** Hypertension Tachycardia Raynaud's phenomenon Psychosis/Mania Hallucinations (auditory, skin sensation, visual disturbance) Anorexia Decreased rate of growth* **Potential Risks** QT prolongation Arrhythmias Ischemic cardiac events Cyanosis Sudden death Cerebrovascular disorders Aggression	V3 was the first RMP to come into effect (V1 and V2 were proposals). Study CRIT124D2201 is ongoing. Drug Utilization Study is planned. Review of FDA/AHRQ sponsored pharmacoepidemiologic initiatives to evaluate adverse cardio-vascular outcomes is ongoing. Educational materials via a website are planned.

RMP Version	RMP Date	Safety Concerns	Comment
		Hostility Depression Suicidality Repetitive behaviors Migraine Tics/Tourette's syndrome/Dystonias Effect on final height* Sexual maturation (delayed)* Drug abuse and drug dependence Withdrawal syndrome Diversion Off-label use Carcinogenicity Cytogenicity Missing Information None (*Risks applicable specifically to the pediatric population)	
4	18-Jan-2010	Lymphocytic leukemia added as a potential risk Neonatal cardio-respiratory toxicity (neonatal/fetal tachycardia, respiratory distress/apnea) added as a potential risk Effects on Neonatal Growth potential added as a potential risk Ischemic cardiac events removed as a potential risk Cytogenicity removed as a potential risk	Study CRIT124D2201 has been completed so it has been removed from the RMP Pharmacovigilance Plan Study CRIT124D2402 (DUS) is now ongoing
5	24-Jan-2011	Aggression changed from potential risk to identified risk Depression changed from potential risk to identified risk Ischemic cardiac events added back in as a potential risk.	The risk of Effects on Neonatal Growth potential in the previous RMP has now been renamed to Effects on Neonatal Growth Study CRIT124D2402 (DUS) was conducted Meta-analysis of MAH data on suicidality added Review of FDA/AHRQ sponsored pharmaco-epidemiologic initiatives to evaluate adverse cardio-vascular outcomes was completed Investigator-initiated/Smoking cessation study in adolescents was added

RMP Version	RMP Date	Safety Concerns	Comment
			Follow-up MTA study ongoing
6.0	07-Dec-2012	No change of safety concerns.	Updated in order to add Adult ADHD indication (Ritalin LA)
6.1	29-May-2014	Cardiomyopathy added as important potential risk	Updated in order to implement commitments requested by BfArM during the EU worksharing procedure to add the Adult ADHD indication (Ritalin LA procedure number DE/H/xxxx/WS/056): Cardiomyopathy added as potential risk Targeted follow-up questionnaires for key cardiovascular concerns of hypertension, tachycardia, QT prolongation and cardiomyopathy were added as tools for enhanced pharmacovigilance
7.0	09-Dec-2014	No change of safety concerns.	Updated clinical data from newly pooled studies and updated Post-marketing data from Periodic Safety Update Report (PSUR) 13
7.1	14-Jul-2015	No change to safety concerns	Changes were made to address the MHRA comments on RMP v7.0 to segregate the safety concerns in pediatric and adult population Table 1-1d in Annex 12 was revised with the inclusion of separate exposure for Studies RIT124D2302 and RIT124D2302E1
7.2	06-Nov-2015	No change to safety concerns	Part II SII: Change made to “Safety pharmacology” in table 3-1 to include alternative wording proposed by the Concerned Member State France on Lead Member State’s assessment report. Part II SVI.1: Detetion of statement regarding the cumulative number of cases of Overdose as per Final WS Var AR.