VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology[1, 2]

The mean worldwide prevalence of ADHD is between 5.29% and 7.1% in children and adolescents (<18 years), meaning that approximately 5-7 out of 100 children and adolescents suffer from this disease worldwide. In Europe, only 5 out of 100 children suffer from ADHD, however there are still few countries which have not provided data for analysis. Estimation of number of children suffering from ADHD may be complicated by a range of factors such as diagnostic method applied and cultural differences.

VI.2.2 Summary of treatment benefits

Methylphenidate is used to treat attention deficit hyperactivity disorder (ADHD) in children and adolescents between 6 and 18 years of age. Such patients have symptoms including short attention span, distractability, emotional lability and moderate to severe hyperactivity. Methylphenidate helps to stabilise these symptoms. It is only used after trying non-medical treatments such as counselling and behavioural therapy, and also forms part of a treatment programme which includes psychological, educational and social therapy.
Methylphenidate improves the activity of certain parts of the brain which are underactive. This helps to improve attention span and concentration, and reduces impulsive behaviour.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
High blood pressure (Hypertension)	Methylphenidate may reduce the effectiveness of drugs used to treat high blood pressure. Methyphenidate can cause sudden blood pressure increase during surgery. Taking methylphenidate with a 'monoamine oxidase inhibitor' (MAOI), used to treat depression, can cause a sudden increase in blood pressure. Patients may commonly experience increased blood pressure whilst taking methylphenidate. Taking an too many tablets of methylphenidate can result in high blood pressure.	Patients who have very high blood pressure or narrowing of the blood vessels, which can cause pain in the arms and legs should not take methylphenidate. Patients should inform their doctor if they have high blood pressure before taking methylphenidate. Patients should not take methylphenidate if they are taking MAOIs. Patients should check with their doctor prior to taking methylphenidate if they are using medicines used to reduce (for example clonidine, guanethidine, verapamil propranolol, etc.) or increase blood pressure (vasopressor agents). Patients should check with their pharmacist before buying any cough or cold remedies as some contain medicines that can effect blood pressure. Patients should tell their doctor if they are going to have a surgery. Methylphenidate should not be taken on the day of a surgery if a certain type of anaesthetic is used. If patients experience an increase in

Risk	What is known	Preventability
		blood pressure whilst taking methylphenidate and it affects them seriously, they should inform their doctor. If patients take too many tablets, then they should inform their doctor or nearest hospital casualty department immediately. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Fast heart beat (Tachycardia)	Patients may commonly experience fast heart beat (tachycardia) whilst taking methylphenidate. Taking too mant tablets of methylphenidate can result in fast heart beat.	If patients experience a fast heart beat whilst taking methylphenidate and it affects them seriously, then they should inform their doctor. If patients take too many tablets, then they should inform their doctor or nearest hospital casualty department immediately. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Numbness, tingling and colour change in fingers and toes when exposed to the cold (Raynaud's phenomenon)	Patients may very rarely experience fingers and toes feeling numb, tingling and changing colour of the skin (from white to blue, then red) when cold ('Raynaud's phenomenon').	If patients experience fingers and toes feeling numb, tingling and changing colour of the skin (from white to blue, then red) when cold and it affects them seriously whilst taking methylphenidate, they should inform their doctor.
Hallucinations (auditory, skin sensation, visual disturbance)	Patients may uncommonly experience seeing, feeling, or hearing things that are not real (hallucinations) whilst taking methylphenidate. Taking too many tablets of methylphenidate can result in seeing, feeling, or hearing things that are not real.	Patients should tell their doctor before taking methylphenidate if they see, hear or feel things that are not there. If patients experience these whilst taking methylphenidate, they should inform their doctor immediately. If patients take too many tablets, then they should inform their doctor or nearest hospital casualty department immediately. An educational tool will be provided to help healthcare professionals in prescribing the drug.

Risk	What is known	Preventability
Severe mental condition in which person loses contact with reality, unable to think and judge clearly (Psychosis)/Mood of excitement, over-activity and uninhibited behaviour (Mania)	Patients may rarely feel unusually excitable, over-active, and uninhibited (mania) whilst taking methylphenidate.	Patients should not take methylphenidate if they feel feel unusually excitable, over-active, and uninhibited. If patients experience this whilst taking methylphenidate, they should inform their doctor immediately. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Loss of apetite (Anorexia)	Patients may commonly experience an eating problem where they do not feel hungry or want to eat (anorexia) whilst taking methylphenidate.	Patients should not take methylphenidate if they suffer from an eating problem where they do not feel hungry or want to eat. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Aggression	Patients may commonly experience a feeling of aggression whilst taking methylphenidate.	Patients should inform their doctor if they have a mental health problem which causes them to be aggressive before taking methylphenidate. If patients experience a feeling of aggression whilst taking methylphenidate, they should inform their doctor if it affects them seriously. Patient should be closely monitored for aggressive behaviour whenever the dose is adjusted and every six months. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Depression	Patients may commonly feel depressed whilst taking methylphenidate. If patients abruptly stop taking methylphenidate then they may feel depressed.	Patients should not take methylphenidate if they suffer from severe depression in that they feel very sad, worthless and hopeless. If patients suffer from mental health problems that cause them to feel depressed, then thery should speak

Risk	What is known	Preventability
		to their doctor before taking methylphenidate. Patients should also discuss with their doctor if they have any family history of depression. Patients should talk to their doctor about stopping treatment with methylphenidate and should not stop taking the product abruptly. If patients experience depression and it affects them seriously whilst taking methylphenidate, they should inform their doctor. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Decreased rate of growth	When used for more than a year, methylphenidate may cause reduced growth in some children. This affects less than 1 in 10 children. There may be lack of weight gain or height growth.	The patient's doctor should carefully watch the patient's height and weight, as well as how well they are eating every 6 months. If the patient is not growing as expected, then their treatment with methylphenidate may be stopped for a short time. An educational tool will be provided to help healthcare professionals in prescribing the drug.

Important potential risks

Risk	What is known
Cardiomyopathy (a disease of the heart muscle)	Patients should not take methylphenidate if they have ever had heart problems - such as a heart attack, uneven heartbeat, pain and discomfort in the chest, heart failure, heart disease or were born with a heart problem and to inform the doctor of any heart condition before starting the treatment. The doctor should check if there is a history of sudden unexplained death in the patient's family, and shoud warn the patient/carer to inform them on symptoms such as difficulty breathing, shortness of breath, chest pain or palpitations experienced during treatment as these may lead to the need to periodically check for these signs at change of dose/every 6 months/every visit and eventually stop treatment if needed. Patients may commonly experience uneven heartbeats (arrhythmia) or racing heartbeats that feel like thumping inside

Risk	What is known
	chest (palpitations), changes in blood pressure or number of heart beats, usually an increase and very rare experience sudden chest pain which may spread to the neck or arm, with a shortness of breath and clammy feeling. These may be signs of a heart attack. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Abnormal heart beat (QT prolongation)	Patients may commonly experience an irregular heartbeat (arrhythmia) whilst taking methylphenidate. If patients take too many tablets of methylphenidate then they may experience an irregular heartbeat. Patients should inform their doctor if it affects them seriously.
Abnormnal blue or purple coloration of the skin (Cyanosis)	There is no reference in the proposed SmPC or PIL about cyanosis; routine pharmacovigilance activities are sufficient for the time being.
Irregular heartbeat (Arrhythmias)	Patients may commonly experience an irregular heartbeat (arrhythmia) whilst taking methylphenidate. If patients take too many tablets of methylphenidate then they may experience an irregular heartbeat. Patients should inform their doctor if it affects them seriously. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Sudden death	Patients mat very rarely experience sudden death whilst taking methylphenidate. Co-administration of methylphenidate with clonidine (a drug used to treat high blood pressure) may result in sudden death. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Chest pain, sudden, unexpected stopping of the heart or heart attack (Ischaemic cardiac events)	Patients may rarely or very rarely experience chest pain due to decreased oxygen getting to the heart (angina), sudden, unexpected stopping of the heart (cardiac arrest) or a heart attack (myocardial infarction) whilst taking methylphenidate. Patients should inform their doctor if it affects them seriously.
Migraine	Patients may experience migraine whilst taking methyphenidate. Patients should inform their doctor if it affects them seriously.
Diseases related to blood vessels supplying the brain (Cerebrovascular disorders)	Patients may experience diseases related to blood vessels supplying the brain (cerebrovascular disorders) whilst taking methylphenidate. Patients should inform their doctor if if they experience paralysis or problems with movement and vision, difficulties in speech (these can be signs of problems with the blood vessels in your brain).

Risk	What is known
	An educational tool will be provided to help healthcare professionals in prescribing the drug.
Repetitive behaviours	Patients may very rarely experience abnormal repetition of doing things over and over again whilst taking methylphenidate.
Aggression (Hostility)	Patients may commonly experience a feeling of aggression whilst taking methylphenidate. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Thoughts of harming or killing oneself (Suicidality)	Patients may very rarely experience suicidal attempts whilst taking methylphenidate. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Tics/Worsening of uncontrolled speech and body movements (Tourette's syndrome)/Muscle contractions causing twisting and repetitive movements or abnormal postures (Dystonias)	Patients may very rarely experience abnormal repetition of doing things over and over again whilst taking methylphenidate. Patients may uncommonly experience worsening of uncontrolled speech and body movements (Tourette's syndrome) whilst taking methylphenidate. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Effect on final height	Prolonged use of methylphenidate may commonly cause reduced growth in children.
Dealyed puberty (Sexual maturation (delayed))	Methylphenidate is usually stopped during or after puberty.
Carcinogenicity	In studies investigating cancer in mice and rats, increased numbers of progressively enlarging and spreading tumours in the liver were seen in male mice.
Lymphocytic leukaemia	Patients may rarely experience a low white blood cell count whilst taking methylphenidate. Patients may also experience an abnormal reduction in the levels of all types of blood cells.
Off-label use	Longstanding abuse of methylphenidate can lead to marked tolerance, psychological dependence, abnormal behaviour, psychotic episodes. Abuse and dependence have been described more often with prolonged release formulations.

Risk	What is known
	An educational tool will be provided to help healthcare professionals in prescribing the drug.
Diversion	Longstanding abuse of methylphenidate can lead to marked tolerance, psychological dependence, abnormal behaviour, psychotic episodes. Abuse and dependence have been described more often with prolonged release formulations. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Drug abuse and Drug dependence	Longstanding abuse of methylphenidate can lead to marked tolerance, psychological dependence, abnormal behaviour, psychotic episodes. Abuse and dependence have been described more often with prolonged release formulations. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Withdrawal syndrome	Severe depression can occur following withdrawal following abusive use. An educational tool will be provided to help healthcare professionals in prescribing the drug.
Neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea)	Cases of respiratory disorders in newborn babies have been reported.
Effects on Neonatal growth (via lactation)	Methylphenidate has been found in the breast milk of a woman taking the drug. There is a report of an infant who experienced decreased weight whilst the mother was taking methylphenidate but recovered and gained weight after the mother discontinued treatment with the drug.

Missing information

Risk	What is known
Long-term safety	Long-term use (more than 12 months) of methylphenidate in children and adolescents has not been systematically studied in clinical trials involving comparsion of methylphenidate therapy to a standard or placebo treatment. An educational tool will be provided to help healthcare professionals in prescribing the drug.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine and the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

Additionally, the CHMP requested that all MAHs of methylphenidate produce the following risk minimisation tools:

- Physician's guide to prescribing, and
- Checklists for actions before prescribing and for ongoing monitoring for prescribers and, if possible, caregivers.

Additional Risk Minimisation Measures for methylphenidate (as requested by the CHMP) are described below:

Safety Concerns addressed by the Educational tool:

- Hypertension
- Tachycardia
- Hallucinations (auditory, skin sensation, visual disturbance)
- Psychosis/Mania
- Anorexia
- Aggression
- Depression
- Decreased rate of growth
- Cardiomyopathy
- Arrhythmias
- Sudden death
- Cerebrovascular disorders
- Hostility
- Suicidality
- Tics/Tourette's syndrome/Dystonias
- Off-label use
- Diversion
- Drug abuse and Drug dependence
- Withdrawal syndrome
- Long-term safety

Objective and Rationale
To educate physicians on the use methylphenidate according to the safety guidance given in the safety sections of the SmPC as requested in the Article 31 referral.

This will be achieved by providing educational tools to aid healthcare providers in ensuring they are well informed and able to use methylphenidate according to the most recent safety information and guidance provided in the SmPC.

Proposed Actions
The scope of this project is strictly medical education. The key messages of this educational tool are as follows:

- Alignment with label regarding diagnosis (DSM-IV criteria), medical history, and comorbidities assessments at baseline for contraindications and values to be monitored, as well as tool for documentation. The goal is to evaluate if the patient is an appropriate candidate for a methylphenidate prescription and characteristics to document before prescription.
- Monitoring during treatment related to safety aspects in the core SmPC 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.

The educational tools has been submitted to Health Authorities for assessment through this RMP. Only the active ingredient methylphenidate is mentioned (no brand names). The focus of the educational tool is the appropriate treatment according to the SmPC for methylphenidate. Safety guidance provided in the educational material is in line with the SmPC for methylphenidate and assist healthcare providers in prescribing methylphenidate.

VI.2.6 Planned post authorisation development plan

No post authorisation development has been planned or been performed.

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

Version 1 has been updated to version 2 in line with the DCP RMS Day 70 Preliminary Assessment Report for Methylphenidate Hydrochloride 5,10 and 20 mg tablet (Methylphenidate hydrochloride), procedure number UK/H/5833/01-03/DC, by Generics (UK) Ltd t/a Mylan.

Version 2 has been updated to version 3 (this version) in line with the DCP RMS Day 120 Draft Assessment Report. The following changes were made during this version of RMP:

1. Cardiomyopathy was included as important potential risk

2. Terminology for important potential risk “Neonatal effects on growth (via lactation)” was revised to “Effects on Neonatal growth (via lactation)”

3. Other necessary changes were made to communication plan, educational materials and cover letter (DHCP) as per the RMS Day 120 draft assessment report