Methylphenidate Actavis

Version 2.0

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Attention deficit hyperactivity disorder (ADHD) is a developmental condition of inattention and distractibility, with or without accompanying hyperactivity.
In Great Britain, occurrence is reported to be less than 1%. However, other studies suggest that the worldwide occurrence of ADHD is between 8% and 12%.
In children, ADHD is 3-5 times more common in boys than in girls.

ADHD is a developmental disorder that requires an onset of symptoms before age 7 years. After childhood, symptoms may persist into adolescence and adulthood, or they may ameliorate or disappear. The percentages in each group are not well established, but at least an estimated 15-20% of children with ADHD maintain the full diagnosis into adulthood. As many as 65% of these children will have ADHD or some residual symptoms of ADHD as adults.[1]

VI.2.2 Summary of treatment benefits

A meta-analysis completed in 2001 included 62 studies involving 2897 participants (children and adolescents) with diagnosis of attention deficit disorder. The outcome measurement demonstrated a significant effect of methylphenidate. However, these apparent beneficial effects are tempered by the lack of robustness of the findings.

In adults with ADHD, twelve studies (2496 patients) were analysed. Methylphenidate was more efficacious than placebo for reducing the severity of ADHD symptoms. This finding was consistent across all studied methylphenidate formulations. Adverse event induced by the discontinuation of the drug was higher with methylphenidate than with placebo.[2]

VI.2.3 Unknowns relating to treatment benefits

According to the SmPC, there is limited information regarding methylphenidate use in children below age of 6 and elderly. However, based on current knowledge, there is no indication to suggest that treatment results would be different in any subgroup of the target population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
High blood pressure (Hypertension)	Analyses of data from studies of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in blood pressure.	Methylphenidate should not be associated with other drugs that may increase blood pressure. It should not be used in patients with already

Risk	What is known	Preventability
		existing heart and vascular problems. Patients should have a careful history (including assessment for a family history of sudden heart or unexplained death) and physical exam to assess for the presence of heart disease, and should receive further specialist heart evaluation if initial findings suggest such history or disease. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.
Fast heart beat (Tachycardia)	Patients using methylphenidate may commonly experience changes in heart beat.	Patients should have a careful history (including assessment for a family history of sudden heart or unexplained death) and physical exam to assess for the presence of heart disease, and should receive further specialist heart evaluation if initial findings suggest such history or disease. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.
Excessively reduced blood flow causing	Fingers and toes feeling numb, tingling and changing colour (from white to blue, then red) when cold ('Raynaud's phenomenon') may	By monitoring early signs

Risk	What is known	Preventability
discolouration of the fingers, toes, and occasionally other areas (Raynaud's phenomenon)	appear very rare during treatment with methylphenidate.	
Seeing, feeling, or hearing things that are not real (Hallucinations (auditory, skin, sensation, visual disturbance))	Psychotic symptoms (seeing, feeling, or hearing things that are not real, believing things that are not true) in children and adolescents without pre-existing of psychotic illness can be caused by methylphenidate at usual doses.	By monitoring early signs
Feeling unusually excited, over-active and un-inhibited, loss of contact with reality (Psychosis/Mania)	In madness patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder. If this kind of symptoms occur, discontinuation of treatment may be appropriate.	Methylphenidate is contraindicated in patients with already existing psychotic disorders.
Eating problem when you do not feel hungry or want to eat (Anorexia)	Patients using methylphenidate may commonly experience eating problems.	During treatment, doctors should carefully watch how well the patients are eating. Methylphenidate is contraindicated in patients with already existing eating problems.
Reduced growth (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. Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children.	Growth (height and weight) should be screened before treatment and should be monitored during treatment with methylphenidate. If patients are not growing as expected, then their treatment with methylphenidate may be stopped for a short time.
Feeling aggressive (Aggression)	The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit.	In case of long-term use (more than 12 months) in children and adolescents, aggressive or hostile behaviour, should be careful monitored.

Risk	What is known	Preventability
Depression	Careful supervision is required during drug discontinuation, since this may unmask depression as well as chronic over- activity. Some patients may require long-term follow up.	Methylphenidate is contraindicated in patients with severe depression (feeling very sad, worthless and hopeless). Patients with depressive symptoms should be screened before treatment and should be monitored during treatment with methylphenidate.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Migraine	Migraine is a known adverse effect for methylphenidate but its frequency cannot be estimated from the available data.
Repetitive behaviours	Doctors should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes. Treatment interruption can be considered.
Part of ECG readout prolonged (QT prolongation)	Heart and vascular status should be screened before and during treatment with methylphenidate.
Blue or purple coloration of the skin or mucous membranes (Cyanosis)	No data available
Irregular heartbeat (Arrhythmias)	Methylphenidate is contraindicated in case of pre-existing potentially life- threatening arrhythmias. Patients should have a careful history (including assessment for a family history of malignant arrhythmia) and physical exam to assess for the presence of heart disease, and should receive further specialist heart evaluation if initial findings suggest such history or disease.
Sudden death	Patients should have a careful history (including assessment for a family history of sudden cardiac or unexplained death) and physical exam. Sudden death has been reported in association with the use of methylphenidate at usual doses in children, some of whom had structural heart abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known structural heart abnormalities, serious heart rhythm abnormalities, or other serious heart problems that may place them at increased vulnerability to adverse effects of a stimulant medicine.
Damaged or diseased blood vessels that supply the heart with blood, oxygen and	Methylphenidate is contraindicated in patients with pre-existing heart and vascular disorders including pain in the centre of the chest, heart attack.

Risk	What is known (Including reason why it is considered a potential risk)
nutrients (Ischaemic cardiac events)	Patients should have a careful history and physical exam to assess for the presence of heart disease and should receive further specialist heart evaluation if initial findings suggest such history or disease.
Brain blood vessels disorders (Cerebrovascular disorders)	Methylphenidate is contraindicated in patients with problems with the blood vessels in the brain - such as a stroke, swelling and weakening of part of a blood vessel (aneurysm), narrow or blocked blood vessels, or inflammation of the blood vessels (vasculitis). Symptoms and signs of brain blood vessels: • paralysis or problems with movement and vision, difficulties in speech • muscle spasms which you cannot control affecting your eyes, head, neck, body and nervous system -due to a temporary lack of blood supply to the brain
Being hostile (Hostility)	Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes. Treatment interruption can be considered.
Thinking about or feeling like killing yourself (Suicidality)	Methylphenidate is contraindicated in case of diagnosis or history of suicidal tendencies. Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician.
Hard-to-control, repeated twitching of any parts of the body or repeating sounds and words / uncontrolled speech and body movements (Tics/Tourette's syndrome/Dystonias)	Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate.
Effect on final height	Patients should have a pre-treatment test and ongoing monitoring for height on a growth chart. Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children. The effects of methylphenidate on final height and final weight are currently unknown and being studied.
Sexual maturation (delayed)	No data available
Potentially causing cancer (Carcinogenicity)	There is information regarding an increased number of malignant liver tumours noted in male mice observed in mouse studies. The significance of this finding to humans is unknown.
Use of methylphenidate for an unapproved indication	Methylphenidate should not be used in children under 6 years of age and in elderly because the safety and efficacy

Risk	What is known (Including reason why it is considered a potential risk)
(Off-label use)	has not been established in these age groups. Methylphenidate should not be used for the prevention and treatment of normal fatigue states.
Use of prescription drugs for recreational purposes (Diversion)	Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate. Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.
Discontinuation syndrome (Withdrawal syndrome)	Careful supervision is required during drug discontinuation, since this may unmask depression as well as chronic over-activity. Careful supervision is required during withdrawal from abusive use since severe depression may occur.
Drug abuse and Drug dependence	Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate. Chronic abuse of methylphenidate can lead to marked physical and psychological dependence with varying degrees of abnormal behaviour. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.
Cancer affecting circulating lymphocytes (Lymphocytic leukaemia)	No data available
Heart and respiratory toxicity in new-born children – fast heart beat, difficulty in breathing in new-born children (Neonatal cardio-respiratory toxicity- neonatal/foetal tachycardia, respiratory distress/apnoea)	Cases of neonatal heart and respiratory toxicity in new-born children, specifically fast heart beat and difficulty in breathing have been reported. Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.
Effect on growth in new-born children (Neonatal effects on growth)	Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

Missing information

Risk	What is known
Effects after long-term use on heart vessels, brain blood vessels and mental health (Long-term cardiovascular effects, Long-term cerebrovascular effects,	The safety and efficacy of long-term use of methylphenidate has not been evaluated in studies. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring for any sign and symptom indicating a heart or vessels disorder, brain blood vessels disorder and mental health problem.

Risk	What is known
Long-term psychiatric effects)	

VI.2.5 Summary of risk minimisation measures by safety concern

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

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.
These additional risk minimisation measures are for the following risks:

- *High blood pressure*
- *Fast heart beat*
- *Seeing, feeling, or hearing things that are not real*
- *Feeling unusually excited, over-active and un-inhibited, loss of contact with reality*
- *Eating problem when you do not feel hungry or want to eat*
- *Reduced growth*
- *Feeling aggressive*
- *Depression*
- *Uneven heartbeat*
- *Sudden death*
- *Damaged or diseased blood vessels that supply the heart with blood, oxygen and nutrients*
- *Brain blood vessels disorders*
- *Being hostile*
- *Thinking about or feeling like killing yourself*
- *Hard-to-control, repeated twitching of any parts of the body or repeating sounds and words / uncontrolled speech and body movements*
- *Use of methylphenidate for an unapproved indication*
- *Use of prescription drugs for recreational purposes*
- *Discontinuation syndrome*
- *Drug abuse and Drug dependence*
- *Effects after long-term use on heart, vessels, brain blood vessels and mental health*

Educational materials for Healthcare Professionals
Objective and justification of why needed Assisting prescribers by reinforcing the recommendation to check the contraindications, regular monitoring and observe the evolution of the safety profile in each patient.
Proposed actions/components Educational materials: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy • Chart for ongoing monitoring during methylphenidate treatment

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for methylphenidate.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	22-06-2015	*Identified Risks* Hypertension Tachycardia Raynaud's phenomenon Hallucinations (auditory, skin, sensation, visual disturbance) Psychosis/Mania Anorexia Decreased rate of growth Aggression Depression *Potential Risks* Migraine Repetitive behaviours QT prolongation Cyanosis Arrhythmias Sudden death Ischaemic cardiac events Cerebrovascular disorders Hostility Suicidality Tics/Tourette's syndrome/Dystonias Effect on final height Sexual maturation (delayed) Carcinogenicity Off-label use Diversion Withdrawal syndrome Drug abuse and Drug dependence Lymphocytic leukaemia Neonatal cardio-respiratory toxicity neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth *Missing information* Long-term cardiovascular effects, Long-term cerebrovascular effects, Long-term psychiatric effects	First version
2.0	xxxx	No changes to the list of safety concerns	The Physician's guide to prescribing was included as an additional RMM