VI.2. Elements for a Public Summary

CONCERTA contains the active substance 'methylphenidate hydrochloride'. The name 'methylphenidate' will also be used in this summary.

VI.2.1. Overview of Disease Epidemiology

Patients with ADHD find it hard to sit still and to concentrate. Patients with ADHD may have difficulty learning and doing homework. They find it hard to behave well at home, at school, or in other places.

Worldwide between 5.29% and 7.1% of children and adolescents (<18 years) have ADHD. ADHD affects approximately 1 in 20 children and adolescents across Europe with many cases persisting into adulthood. Generally, boys are more likely to be affected than girls.

VI.2.2. Summary of Treatment Benefits

CONCERTA is used to treat attention-deficit/hyperactivity disorder (ADHD). It is used in children between the ages of 6 and 17 years. However, some patients may continue taking CONCERTA into adulthood. CONCERTA is used only after trying treatments that do not involve medicines such as counselling and behavioural therapy.

CONCERTA stimulates activity in certain parts of the brain that are under-active and can help improve attention, concentration, and impulsive behaviour. CONCERTA is given as part of a treatment programme, which usually includes psychological, educational, and social therapy.

CONCERTA was shown to be better than placebo (a sugar pill) for treating the symptoms of ADHD (that is improving attention and behaviour) in 2 studies, and was shown to improve attention similar to other medicines that are used to treat ADHD in 3 studies.

VI.2.3. Unknowns Relating to Treatment Benefits

More information is needed about the long-term effects of CONCERTA, including effects on the heart and blood vessels and on a part of the brain (the cerebrum) and its blood vessels and about the long-term mental and emotional effects, and effects on behaviour. Studies are being conducted to obtain this information. See Section VI.2.6.

VI.2.4. Summary of Safety Concerns

Important Identified Risks

Risk	What is known	Preventability
High blood pressure (Hypertension)	High blood pressure is a common side effect of CONCERTA (may affect up to 1 in 10 people)	CONCERTA must not be given to a patient who: • has very high blood pressure or narrowing of the blood vessels, which can cause pain in the arms and legs • has ever had heart problems - such as a heart attack, uneven heartbeat, pain and discomfort in the chest, heart failure, heart disease or was born with a heart problem • has a thyroid problem • has a tumour in the adrenal gland that makes lots of adrenaline (phaeochromocytoma) • is currently taking or has taken within the last 14 days a specific antidepressant (known as a monoamine oxidase inhibitor) Extra care is needed in giving CONCERTA to patients who have medical conditions that might be made worse by increases in blood pressure or heart rate. Blood pressure and pulse should be checked by the patient's doctor at each change of dose and then at least every 6 months.
Fast heart beat (Tachycardia)	Fast heart beat is a common side effect of CONCERTA (may affect up to 1 in 10 people).	CONCERTA must not be given to a patient who: • has ever had heart problems - such as a heart attack, uneven heartbeat, pain and discomfort in the chest, heart failure, heart disease or was born with a heart problem • has a thyroid problem • has a tumour of the adrenal gland that makes lots of adrenaline (phaeochromocytoma) • is currently taking or has taken within the last 14 days a specific antidepressant (known as a monoamine oxidase inhibitor) Patients who develop symptoms of heart disease during CONCERTA treatment should be seen by a heart specialist.
Fingers and toes feeling numb, tingling and changing colour (from white to blue, then red) when cold (Raynaud's phenomenon)	Raynaud's phenomenon is a very rare side effect of CONCERTA (may affect up to 1 in 10,000 people).	Preventive steps include dressing in layers or wearing gloves or heavy socks to keep warm.

Risk	What is known	Preventability
Seeing, feeling, or hearing things that are not real (Hallucinations [auditory, skin sensation, visual disturbance])	Seeing, feeling, or hearing things that are not real is an uncommon side effect of CONCERTA that could be serious (may affect up to 1 in 100 people).	CONCERTA must not be given to patients with or who have had mental health problems such as: • a 'psychopathic' or 'borderline personality' problem • abnormal thoughts or visions or an illness called 'schizophrenia' • signs of a severe mood problem like: - feeling like killing yourself - feeling very sad, worthless and hopeless - feeling unusually excitable, over-active, and uninhibited. Mental health problems should be monitored by a patient's doctor at every change of dose, then at least every 6 months and at every visit. CONCERTA treatment may need to be stopped. If a patient sees, feels, or hears things that are not real, their parent should contact the doctor straight away.
Believing things that are not true or a break from reality/feeling unusually excited, overactive and uninhibited (Psychosis/Mania)	Treatment with CONCERTA may cause or make symptoms of psychosis worse. Feeling unusually excited, overactive and uninhibited is a rare side effect of CONCERTA that could be serious (may affect up to 1 in 1,000 people).	CONCERTA must not be given to patients with or who have had mental health problems such as: • a 'psychopathic' or 'borderline personality' problem • abnormal thoughts or visions or an illness called 'schizophrenia' • signs of a severe mood problem like: - feeling like killing yourself - feeling very sad, worthless and hopeless - feeling unusually excitable, over-active, and un-inhibited. Mental health problems should be monitored by a patient's doctor at every change of dose, then at least every 6 months and at every visit. CONCERTA treatment may need to be stopped. Extra care is needed by a doctor when giving CONCERTA to patients with bipolar disorder because these patients are at an increased risk of mania (feeling unusually excited, overactive and uninhibited). If a patient is feeling unusually excited, overactive, and uninhibited, their parent should contact the doctor straight away. If symptoms of psychosis or mania occur, treatment with CONCERTA may need to be stopped. If a patient sees, feels, or hears things that are not real, their parent should contact the doctor straight away.

Risk	What is known	Preventability
Loss of appetite or decreased appetite (Anorexia)	Loss of appetite or decreased appetite is a common side effect of CONCERTA (may affect up to 1 in 10 people).	CONCERTA must not be given to patients with or who have had an eating problem that means they do not feel hungry or want to eat - such as 'anorexia nervosa'. Mental health problems should be monitored by a patient's doctor at every change of dose, then at least every 6 months and at every visit. CONCERTA treatment may need to be stopped.
Lack of weight gain or height growth (Decreased rate of growth)	When used for more than a year, CONCERTA may cause reduced growth in some children (may affect fewer than 1 in 10 people).	The doctor should carefully monitor a patient's height and weight, and how well they are eating. If a patient is not growing as expected, treatment with CONCERTA may be stopped for a short time.
Feeling aggressive (Aggression)	Feeling aggressive is a common side effect of CONCERTA (may affect 1 in 10 people).	CONCERTA must not be given to patients with or who have had mental health problems such as: • a 'psychopathic' or 'borderline personality' problem • abnormal thoughts or visions or an illness called 'schizophrenia' • signs of a severe mood problem like: - feeling like killing yourself - feeling very sad, worthless and hopeless - feeling unusually excitable, over-active, and un-inhibited. Patients treated with CONCERTA should be closely checked by their doctor for aggressive behaviour or hostility when treatment is started, at every change of dose, and then at least every 6 months and every visit. The doctor may change the dose of or stop CONCERTA treatment.
Feeling depressed (Depression)	Feeling depressed is a common side effect of CONCERTA (may affect 1 in 10 people).	CONCERTA must not be given to patients with or who have had mental health problems such as: • a 'psychopathic' or 'borderline personality' problem • abnormal thoughts or visions or an illness called 'schizophrenia' • signs of a severe mood problem like: - feeling like killing yourself - feeling very sad, worthless and hopeless - feeling unusually excitable, over-active, and un-inhibited.

Risk	What is known	Preventability
Feeling depressed (Depression)		Mental health problems should be monitored by a patient's doctor at every change of dose, then at least every 6 months and at every visit. CONCERTA treatment may need to be stopped.
Damage to the liver caused by medication	Increases in liver enzymes is an uncommon side effect of CONCERTA (may affect 1 in 100 people). Coma due to liver failure occurs very rarely in patients taking CONCERTA(may affect 1 in 10,000 people).	Because predisposition to liver damage depends on many things (eg. age, sex, other medications patients are taking, alcohol use, any already existing liver problems) because liver damage occurs very rarely doctors have limited actions they can take to prevent liver injury.
Persistent and painful erection of the penis (Priapism)	Priapism as an ADR is reported very rarely in patients taking CONCERTA (may affect 1 in 10,000 people).	If a patient has persistent and painful erection of the penis, he or his parent/s should contact the doctor straight away.

Important Potential Risks

Risk	What is known (Including reason why it is considered a potential risk)
Migraine	CONCERTA does not seem to cause migraine. Since CONCERTA decreases appetite it may increase the number of headaches in patients who get migraines.
Doing things over and over again (Repetitive behaviours)	The risk of repetitive behaviours during CONCERTA treatment is very small. Repetitive behaviours have been reported by people taking medicines (like methylphenidate) that stimulate the brain.
An increase in the time it takes for the heart muscle to contract and then relax. This is reported on an electrical tracing of heart activity (QT prolongation)	This can cause the heart to have a serious problem in which it beats too fast or unevenly, or even stops beating. There is no clear evidence that medicines like CONCERTA are associated with this problem.
Bluish or purplish colour of the skin usually due to due to a low level of oxygen in the blood (Cyanosis)	CONCERTA does not seem to cause cyanosis, but it may make this condition worse in patients who already have this problem. Cyanosis has been reported by people taking medicines like methylphenidate that stimulate the brain.
A problem with the speed or rhythm of the heartbeat (Arrhythmias)	Arrhythmia is a very rare side effect of treatment in healthy patients who are given the approved doses of CONCERTA. If a patient becomes aware of their heartbeat (palpitations) or has an uneven heartbeat (arrhythmia), they or their parent should contact the doctor straight away.

Risk	What is known (Including reason why it is considered a potential risk)
Sudden death	Sudden death has been reported with the use of medicines like methylphenidate that stimulate the brain in children including some who already had serious heart problems. This type of medicine is not to be given to children or adolescents with serious heart problems.
Effects when heart muscle does not get enough oxygen (Ischaemic cardiac events)	There have been a few cases of ischaemic cardiac events in children and adolescents with ADHD being treated with CONCERTA. If a patient has symptoms of a possible heart attack or other heart problem, such as unexplained fainting, chest pain, or shortness of breath, they or their parent should contact the doctor straight away.
Effects on the blood vessels or blood supply of the brain (stroke or mini-stroke) (Cerebrovascular disorders)	There have been a few cases of stroke or mini-stroke in patients with ADHD being treated with CONCERTA. CONCERTA must not been given to a patient with a problem 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). If a patient has paralysis or problems with movement and vision, difficulties in speech (which can be signs of problems with the blood vessels in the brain) or muscle spasms which they cannot control affecting their eyes, head, neck, or body (which may be due to a temporary lack of blood supply to the brain), they or their parent should contact the doctor straight away.
Anger towards other people (Hostility)	The use of medicines like methylphenidate that stimulate the brain may also make the expression of hostile behaviour easier. Patients treated with CONCERTA should be closely checked by their doctor for aggressive behaviour or hostility when treatment is started, at every change of dose, and then at least every 6 months and every visit. The doctor may change the dose of or stop CONCERTA treatment.
Thinking about or feeling like killing yourself, suicidal attempt (Suicidality)	Patients with ADHD may have a higher risk for thinking about suicide or trying to commit suicide-related behaviour. Patients who experience this during treatment with CONCERTA should be seen by their doctor immediately. Treatment with CONCERTA may need to be stopped.
Hard-to-control, repeated twitching of any parts of the body or repeating sounds and words/uncontrolled speech and body movements/involuntary muscle contractions causing uncontrollable movements (Tics/Tourette's syndrome/Dystonias)	New or worsening tics and worsening of Tourette's syndrome are side effects of CONCERTA. Patients should be checked regularly by their doctor for new or worsening tics during treatment with CONCERTA. Patients should be checked at every change of dose and then at least every 6 months or every visit. If a patient has uncontrolled speech and body movements (Tourette's syndrome), their parent should contact the doctor straight away.
Effect on final height	When used for more than a year, CONCERTA may cause reduced growth in some children. Because of this reduced growth, it is possible (but not proven) that a child's final height may be reduced.

Risk	What is known (Including reason why it is considered a potential risk)
	However, the effects of CONCERTA on final height and final weight are currently unknown and being studied.
Delayed puberty and sexual development (Sexual maturation [delayed])	When used for more than a year, CONCERTA may cause reduced growth in some children. Because of this reduced growth, it is possible (but not proven) that a child's puberty and their sexual development may be delayed.
Cancer (Carcinogenicity)	An early study of methylphenidate in children found effects suggesting that CONCERTA might be linked with the development of cancer. However, recent studies have not shown these effects. In studies in rats and mice given methylphenidate, increased numbers of malignant liver tumours were only seen in male mice. It is not known if this means there is a risk for humans.
Use of CONCERTA other than for an approved use (Off-label use)	Sometimes CONCERTA is prescribed to treat medical conditions other than ADHD (the label approves CONCERTA for the treatment of ADHD).
Transfer of CONCERTA from a legal to an illegal channel of distribution or use (Diversion)	CONCERTA is a controlled substance, which means that its possession and use are controlled by law. As with any controlled substance, there is a risk of children using CONCERTA for recreational purposes (a "high") or giving CONCERTA to other people. Patients should be carefully monitored by their doctor for diversion of CONCERTA. CONCERTA should be given with caution to patients with known drug or alcohol dependency.
Side effects when treatment is stopped (Withdrawal syndrome)	Careful supervision by a patient's doctor is required when people who have abused CONCERTA stop taking it because depression or over-activity may occur. Careful supervision by a patient's doctor is required when people who have abused CONCERTA stop taking it since severe depression may occur.
Drug abuse and Drug dependence	Patients should be carefully monitored by their doctor for misuse of CONCERTA. CONCERTA should be given with caution to patients with known drug or alcohol dependency or to emotionally unstable patients. Abuse of CONCERTA over a long time can lead to the medicine becoming less effective (you become tolerant to the medicine) and dependence with abnormal behaviour including psychosis (believing things that are not true or a break from reality).
A type of cancer of the blood and bone marrow (Lymphocytic leukaemia)	In one study, there was an increased risk of lymphatic leukaemia with methylphenidate use. The need for continuing drug treatment should be reviewed by a doctor from time to time.

Risk	What is known (Including reason why it is considered a potential risk)
Effects on the heart and lungs of newborns of mothers treated with CONCERTA (Neonatal cardio-respiratory toxicity [neonatal/foetal tachycardia, respiratory distress/apnoea])	Cases of fast heart beat in unborn or newborn babies and difficulty breathing in newborn babies have been reported. CONCERTA is not recommended for use during pregnancy unless a patient's doctor decides that the benefit of taking methylphenidate during pregnancy is greater than the risks that may occur if the mother does not take the medicine.
Effects on the growth of newborns of mothers treated with CONCERTA (Neonatal effects on growth)	There is one report of an infant who had a decrease in weight but recovered and gained weight after the mother stopped treatment with methylphenidate. Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. A decision by the doctor must be made whether to stop breast-feeding or to stop methylphenidate treatment taking into account the benefit of breast-feeding for the child and the benefit of treatment for the woman.

Missing Information

Risk	What is known
Long-term effects on the heart and blood vessels (Long-term cardiovascular effects)	The long-term use of methylphenidate has not been studied in clinical trials. CONCERTA must not be given to patients with certain conditions affecting the heart and blood vessels. Patients treated for more than 12 months must be carefully reviewed by their doctor.
Long-term effects on a part of the brain (the cerebrum) and its blood vessels (Long-term cerebrovascular effects)	The long-term use of methylphenidate has not been studied in clinical trials. CONCERTA must not be given to patients who have had a problem 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). Patients on long-term therapy (over 12 months) must be carefully reviewed by their doctor.
Long-term mental, emotional, and behavioural effects (Long-term psychiatric effects)	The long-term use of methylphenidate has not been studied in clinical trials. CONCERTA must not be given to patients with or who have had certain psychiatric conditions (see earlier information for Hallucinations [auditory, skin sensation, visual disturbance], Psychosis/Mania, Aggression, Depression, Hostility, and Suicidality). Patients treated for more than 12 months must be carefully reviewed by their doctor.

VI.2.5 Summary of Additional Risk Minimisation Measures by Safety Concern

All medicines in the European Union have a Summary of Product Characteristics (SmPC) which provides doctors, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. This information is provided to patients in the Package Leaflet. The details in these documents are known as 'routine risk minimisation measures'.

The SmPC and Package Leaflet for CONCERTA can be found on the website of the European Medicines Agency (EMA). The EMA is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). These measures are summarised below.

Safety Concern (medical term)

- High blood pressure (Hypertension)
- Fast heart beat (Tachycardia)
- Seeing, feeling, or hearing things that are not real (Hallucinations [auditory, skin sensation, visual disturbance])
- Believing things that are not true or a break from reality/feeling unusually excited, overactive, and uninhibited (Psychosis/Mania)
- Loss of appetite or decreased appetite (Anorexia)
- Lack of weight gain or height growth (Decreased rate of growth)
- Feeling aggressive (Aggression)
- Feeling depressed (Depression)
- A problem with the rate or rhythm of the heartbeat (Arrhythmias)
- Sudden death
- Effects when heart muscle does not get enough oxygen (Ischaemic cardiac events)
- Effects on the blood vessels or blood supply of the brain (Cerebrovascular Disorders)
- Hostility
- Thinking about or feeling like killing yourself, suicidal attempt (Suicidality)
- Hard-to-control, repeated twitching of any parts of the body or repeating sounds and words/uncontrolled speech and body movements/involuntary muscle contractions causing uncontrollable movements (Tics/Tourette's syndrome/Dystonias)
- Use of CONCERTA other than for an approved use (Off-label use)
- Transfer of CONCERTA from a legal to an illegal channel of distribution or use (Diversion)
- Side effects when treatment is stopped (Withdrawal syndrome)
- Drug abuse and Drug dependence
- Long-term effects on the heart and blood vessels (Long-term cardiovascular effects)
- Long-term effects on a part of the brain (the cerebrum) and its blood vessels (Long-term cerebrovascular effects)
- Long-term mental, emotional, and behavioural effects (Long-term psychiatric effects)

Risk Minimisation Measure(s): Educational tool
Objective and rationale: To educate doctors on the safe use of methylphenidate. This is achieved by providing core educational tools to aid healthcare providers in ensuring they are well informed and able to use methylphenidate according to the most recent safety information.
• Summary description of main additional risk minimisation measures Educational tools to help doctors, pharmacists, and other health care professionals correctly use methylphenidate for ADHD are available on a website (this is the educational tool). The content of the website is available in the 23 official EU languages. The information on the website is available for download and incorporation within individual patient records.

VI.2.6 Planned Postauthorisation Development Plan

List of Studies in Postauthorisation Development Plan

Study/activity (including study number)	Objectives	Safety concerns/ efficacy issue addressed	Status (planned, started)	Date for submission of (interim and) final results
Multimodal Treatment Study (MTA) funded by the National Institute of Mental Health	Evaluated the leading treatments for ADHD including behaviour therapy, medications, and the combination of the two over 14 months.	The Important Identified Risk of Decreased rate of growth, and the Important Potential Risks of Effect on final height and Sexual maturation (delayed)	Long-term follow up is ongoing.	Per Article 31, the company will review the publications for safety information. (Other published results have been reported in the EU RMP.)
Attention Deficit Hyperactivity Drugs Use Chronic Effects (ADDUCE) studies funded by the European Commission	To evaluate the long-term effects of taking methylphenidate	Missing Information Long-term cardiovascular effects Long-term cerebrovascular effects Long-term psychiatric effects	Ongoing These studies are expected to be completed November 2015 and publication will follow shortly thereafter.	Per Article 31, the company will review the publications for safety information.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

The Risk Management Plan is a document that describes what is known and not known about the safety of a medicine, and how to prevent or manage the risks to the patients who take that medicine. It is updated throughout the lifetime of the medicine, as new information becomes available.

This section summarises the changes to the Risk Management Plan for CONCERTA.

Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	16/10/2008	Original version of Risk Management Plan	
2.0	23/11/2009	In a report from the UK Medicines and Healthcare Products Regulatory Agency Assessment (MHRA) Report dated 3 December 2008, the core table of risks was updated to include the following 3 potential risks: • Lymphocytic leukaemia • Neo-natal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea • Neonatal effects on growth ("via lactation" added in parenthesis by the Company) Also, the seventh potential risk is termed "Cerebrovascular disorders" and long-term safety was identified as an area of Missing Information.	In order to sell CONCERTA in the European Union, the company must include all of the risks required by the Health Authority in the EU in the CONCERTA product information.
3.0	30/11/2010	This Risk Management Plan update addresses the requests from PSUR Reference Member State's (Medicines and Healthcare products Regulatory Agency) Assessment Report dated 23 September 2010 that included the following requests: • Ischaemic cardiac events was designated a new potential risk (not previously included in the CONCERTA Risk Management Plan) • Aggression and depression were designated as identified risks (formerly potential risks) • Missing Information regarding long-term safety related to the key risks of cardiovascular, cerebrovascular, and psychiatric effects was added.	

Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
3.0	30/11/2010	The potential risk of Neonatal effects on growth (via lactation) was revised by deletion of "(via lactation)" for consistency with the name of this risk in the Assessment Report. Requests were also received for revisions to the planned educational tool.	
4.0	11/12/2012	No change to the risk management plan. A study found no increased risk for serious cardiovascular events (ie, sudden cardiac death, acute myocardial infarction, and stroke) in children and young adults who were receiving an ADHD drug. The results of a meta-analysis for suicidality demonstrate that methylphenidate does not seem to increase the risk of suicide or self-harm-related events relative to placebo in children and adolescents with ADHD.	The description of cardiovascular and suicidality risks in the CONCERTA Risk Management Plan, SmPC, and Package Leaflet is adequate and no changes to this description are needed. This version was submitted but was never reviewed by EMA..
5.0	22/04/2014	Priapism (persistent and painful erection of the penis) was added as a new Important Identified Risk.	The DHPC was distributed prior to the completion of this RMP update. This version was submitted but was never reviewed by EMA.
6.0	22/04/2016	Priapism (persistent and painful erection of the penis) was deleted as an Important Identified Risk. Drug-Induced Liver Injury was added as a new Important Identified Risk.	The proposed risk was not accepted by the MHRA which is the reference member state for methylphenidate in the EU
7.0	18/10/2016	Priapism (persistent and painful erection of the penis) was added as an Important Identified Risk.	The final PSUSA assessment report (PSUSA procedure PSUSA/00002024/201510) requested the RMP be updated with the new signal. PRAC is reviewing Priapism separately as a potential signal.