PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for CONCERTA (Methylphenidate Hydrochloride)

This is a summary of the Risk Management Plan (RMP) for CONCERTA. The RMP details important risks of CONCERTA, how these risks can be minimized, and how more information will be obtained about CONCERTA's risks and uncertainties (missing information).

CONCERTA's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how CONCERTA should be used.

Important new concerns or changes to the current ones will be included in updates of CONCERTA's RMP.

I. The Medicine and What It Is Used For

CONCERTA is authorized for attention deficit hyperactivity disorder (ADHD) (see SmPC for the full indication). It contains methylphenidate hydrochloride as the active substance and it is given orally by prolonged-release tablets.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of CONCERTA, together with measures to minimize such risks and the proposed studies for learning more about CONCERTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CONCERTA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of CONCERTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CONCERTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important Identified Risks	• Serious cardiovascular events • Reduced weight gain (pediatric indication only) • Decreased rate of growth (pediatric indication only)
Important Potential Risks	• Sexual maturation delayed (pediatric indication only)
Missing Information	• Long-term effects

II.B. Summary of Important Risks

The safety information in the Product Information is aligned to the reference medicinal product.

Important Identified Risk: Serious Cardiovascular Events	
Evidence for linking the risk to the medicine	Cases of serious cardiovascular events have been reported in clinical trials and the postmarketing setting, and cases of sudden death have also been reported in the postmarketing setting. Cardiovascular events are described in the current prescribing information for CONCERTA.
Important Identified Risk: Serious Cardiovascular Events	
Risk factors and risk groups	Age is an independent risk factor for cardiovascular disease in adults, and these risks may be compounded by additional factors including frailty, obesity and diabetes (Rodgers 2019). General risk factors for hypertension in adults include older age, race (African heritage), being overweight or obese, physical inactivity, family history of high blood pressure, tobacco and alcohol use, and stress (Mayo Clinic 2021). General risk factors for hypertension in children include being overweight or obese, family history of high blood pressure, type 2 diabetes or a high fasting blood sugar level, and high cholesterol and triglycerides (Mayo Clinic 2018). In adults, causes of arrhythmia include coronary artery disease, hypertension, cardiomyopathy, valve disorders, electrolyte imbalances in the blood (including sodium or potassium), injury from a heart attack, and post-heart surgery (Cleveland Clinic 2018). Causes of arrhythmias in children include cardiomyopathy or congenital heart disease. Other common causes are infections, chemical imbalances, fever, and certain medications (Cleveland Clinic 2011). Long QT syndrome can be inherited and is also more common in children who are born deaf.

	In boys, the QT intervals often return toward normal after puberty (NHLBI 2013). In addition, children and teenagers who experience unexplained fainting, near drownings, or other accidents, and unexplained seizures may also be at risk. Medications known to prolong QT intervals, and eating disorders, such as anorexia, can also contribute to increased risk (Mayo Clinic 2012). Atrial tachyarrhythmias are most commonly seen in children with congenital heart disease in whom cardiac surgery has been performed. According to a German study (Grosse-Wortmann 2010) of 494 neonates and older children during first 72 hours after surgery for congenital heart disease found that for neonates, male sex and longer cross-clamping time independently increased risk for arrhythmias. Ventricular septal defect repair was a strong risk factor for junctional ectopic tachycardia in neonates and in older children. Finally, older age and closure of atrial septic defects predisposed infants and children to arrhythmias of any type. Risk factors for ischemic cardiac events include physical inactivity, smoking, high blood cholesterol and other lipids, high blood pressure, diet, excess weight and obesity, and diabetes mellitus (Lloyd-Jones 2010). Risk factors in children include a history of familial hypercholesterolemia and a family history of early coronary heart disease (Dadfarmay 2009). Long-standing hypertension and myocardial infarction (ischemic myopathy) are known risk factors for developing cardiomyopathy. Literature per Cooper et al (Cooper 2011) concluded that among young and middle-aged adults (ages 25 to 64 years) current or new use of ADHD medication was not associated with an increased risk of Serious cardiovascular events. However, hypertensive heart disease (or long-standing hypertension) can manifest as left
Important Identified Risk: Serious Cardiovascular Events	
	ventricular hypertrophy with isolated diastolic dysfunction and preserved systolic function. Due to remodeling over time, the hypertrophy can progress to a dilated cardiomyopathy with systolic dysfunction. Although hypertrophic cardiomyopathy is usually inherited, it can also develop from long standing hypertension. Patients who are using CONCERTA long term into adulthood could have a risk of developing high blood pressure, and/or myocardial infarction, therein also theoretically having a potential risk of developing cardiomyopathy. The incidence rates for sudden cardiac death and sudden unexpected death increase with age and they were found to be higher in boys/men than girls/women in all age groups and populations. Known risk factors for cardiovascular disease include cigarette smoking, hypertension, physical inactivity, obesity, dyslipidemia, hyperinsulinemia, homocysteinemia, and poor nutrition. ADHD has not been identified as a risk factor in sudden death. However, it is believed that patients with structural cardiac abnormalities may be at a greater risk of sudden death when treated with CONCERTA. For instance, a matched case-control study investigating 564 cases of sudden death occurring at ages 7 to 19 years across the United States matched to 564 subjects dying in motor vehicle accidents observed

	that 1.8% of sudden deaths were in youths taking stimulants compared to 0.4% in the control group. Hence, a significant association of stimulant use with sudden death was concluded based on exact conditional logistic regression (odds ratio 7.4; 95% confidence interval [CI]: 1.4 to 74.9) (Gould 2009).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	• Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) studies
Important Identified Risk: Reduced Weight Gain (pediatric indication only)	
Evidence for linking the risk to the medicine	Cases of reduced weight gain have been reported in clinical trials and the postmarketing setting, and reduced weight gain is described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Data available from CONCERTA clinical trials do not indicate that any group is at particular risk for reduced weight gain.
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.3, 4.4, 4.8 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	• ADDUCE studies
Important Identified Risk: Decreased Rate of Growth (pediatric indication only)	
Evidence for linking the risk to the medicine	Cases of decreased rate of growth have been reported in the postmarketing setting, and decreased rate of growth is described in the current prescribing information for CONCERTA.
Risk factors and risk groups	Many factors affect rate of growth, with genetics playing a prominent role. Short stature is most commonly of genetic determination and correlates well with parental stature. Additional factors for delayed or slower-than-expected growth could include chronic disease, endocrine disorders, emotional health, infection, and poor nutrition (Medline Plus 2013a).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.4, 4.8 • Patient Leaflet Sections 3, 4 **Additional risk minimization measures:** • None

Additional pharmacovigilance activities	• ADDUCE studies
Important Potential Risk: Sexual Maturation Delayed (pediatric indication only)	
Evidence for linking the risk to the medicine	Cases of delayed sexual maturation have been reported in the postmarketing setting.
Risk factors and risk groups	Common causes of delayed sexual maturation include ovarian failure, constitutional delay, psychological and nutritional factors, illicit drugs (such as marijuana), endocrine-related factors (such as thyroid dysfunction, Cushing's syndrome, prolactinomas, congenital adrenal hyperplasias, diabetes mellitus), gonadotropin-releasing hormone deficiency, hypopituitarism, congenital central nervous system defects, benign or malignant pituitary lesions, craniopharyngioma, mullerian agenesis, vaginal septum, imperforate hymen, and androgen insensitivity syndrome (Maharaj 2012).
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2 and 4.4 **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	• ADDUCE studies
Missing Information: Long-term Effects	
Risk minimization measures	**Routine risk minimization measures:** • SmPC Sections 4.2, 4.4 • Patient Leaflet Sections 2, 4 **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	• ADDUCE studies

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of CONCERTA.

II.C.2. Other Studies in Postauthorization Development Plan

ADDUCE Studies

Purpose of the study: Marketing Authorization Holders are required to evaluate the publications of the ADDUCE studies to determine if they provide additional pharmacovigilance information for the long-term Missing Information.