13 Part VI: Summary of the risk management plan for Ritalin/ Ritalin LA

This is a summary of the risk management plan (RMP) for Ritalin/ Ritalin LA. The RMP details important risks of Ritalin, how these risks can be minimized, and how more information will be obtained about Ritalin's risks and uncertainties (missing information).

Ritalin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ritalin should be used.

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

13.1 Part VI: I. The medicine and what it is used for

Ritalin is indicated in Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 years and older (Ritalin and Ritalin LA) and narcolepsy (Ritalin). It is also indicated in ADHD in adults (Ritalin LA only). It contains methylphenidate as the active substance and is given by oral route to patients in tablet (10 mg) and LA capsule form (10 mg, 20 mg, 30 mg, 40 mg, and 60 mg).

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Ritalin together with measures to minimize such risks and the proposed studies for learning more about Ritalin'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 package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 (e.g. 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 PSUR 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 Ritalin/ Ritalin LA is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Ritalin 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 Ritalin. 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 (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information (Adult and pediatric population)

Important identified risks	Serious Cardiovascular events
	Psychosis/mania
	Verbal and Motoric tics
	Depression
	Aggression
	Drug abuse and drug dependence
	Decreased rate of growth*
	Reduced weight gain*
	Cerebrovascular disorders
	Neonatal toxicity**
	Seizures
	Withdrawal syndrome
Important potential risks	Sexual maturation (delayed)*
	Suicidality
Missing information	Long-term effects

* only relevant for pediatric populations
** only relevant for adult populations

13.2.2 Part VI – II B: Summary of important risks

Table 13-2 Important identified risk: Serious cardiovascular events: Arrhythmias

Evidence for linking the risk to the medicine	Current evidence is based on 193 Ritalin and 21 Focalin cases retrieved cumulatively. The reporting rate of arrhythmia as of 31-Oct-2021: Ritalin 133.04 cases/million PTY; Focalin, 28.41 cases/million PTY With no strong evidence for mechanism of action the strength of evidence is considered weak.
Risk factors and risk groups	Risk factors/groups include: idiopathic degeneration, some illegal and prescribed drugs (e.g. amphetamines, cocaine, beta-blockers, psychotropics and sympathomimetics), hypothyroidism, advanced liver disease, hypothermia, typhoid fever, brucellosis, myocardial infarction, coronary spasm, acute infections, blood chemistry imbalances, endocrine abnormalities, history of heart attacks. Arrhythmia may also occur during episodes of vasovagal syncope, severe hypoxia, hypercapnia, anemia and acute hypertension.

Risk minimization measures	**Routine risk minimization measure** SmPC: Contraindications (Section 4.3) SmPC: Warning (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

PTY = patient treatment-years

Table 13-3 Important identified risk: Serious cardiovascular events: Sudden death

Evidence for linking the risk to the medicine	Current evidence is based on 36 Ritalin and 5 Focalin cases retrieved cumulatively. The reporting rate of Sudden death as of 31-Oct-2021: Ritalin – 2.85 cases/million PTY; Focalin - 0.96 cases/million PTY. With no strong evidence for mechanism of action and no cases in the clinical trial setting have been reported, the strength of evidence is considered weak
Risk factors and risk groups	The incidence rates for SCD increases with age and it was found to be higher in males than females 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.
Risk minimization measures	**Routine risk minimization measure** SmPC: Contraindications (Section 4.3) SmPC: Warnings (Section 4.4) SmPC: Interactions (Section 4.5) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-4 Important identified risk: Serious cardiovascular events: Ischemic cardiac events

Evidence for linking the risk to the medicine	Current evidence is based on 101 Ritalin and 5 Focalin cases retrieved cumulatively with no strong evidence for mechanism of action and unlistedness, the strength of evidence is considered weak. The reporting rate of ischemic cardiac events as of 31-Oct-2021: Ritalin 13.79 cases/million PTY; Focalin 1.73 cases/million PTY.
Risk factors and risk groups	Risk factors include: hypertension, cigarette smoking, diabetes, high fat diet, high cholesterol, obesity, and personal or family history of heart attack, angina, atherosclerosis or other coronary artery diseases.

Risk minimization measures	**Routine risk minimization measure** SmPC: Contraindications (Section 4.3) SmPC: Warning (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-5 Important identified risk: Serious cardiovascular events: Cardiomyopathy

Evidence for linking the risk to the medicine	Current evidence is based on 34 Ritalin cases and 2 Focalin cases retrieved cumulatively with no strong evidence for mechanism of action, and no cases in the clinical trial setting have been reported; hence, the strength of evidence is considered weak.
Risk factors and risk groups	• A family history of cardiomyopathy, heart failure, or sudden cardiac arrest (SCA) • A disease or condition that can lead to cardiomyopathy, such as coronary heart disease, heart attack, or a viral infection that inflames the heart muscle • Diabetes or other metabolic diseases, or severe obesity • Diseases that can damage the heart, such as hemochromatosis, sarcoidosis, or amyloidosis • Long-term alcoholism • Long-term high blood pressure Primarily due to genetic defects or secondarily as a consequence of multiple factors (infections, toxins, alcohol, drugs, metals, autoimmune, etc.).
Risk minimization measures	**Routine risk minimization measure** None **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-6 Important identified risk: Psychosis/mania

Evidence for linking the risk to the medicine	Current evidence is based on 916 Ritalin cases and 105 Focalin cases retrieved for psychosis and 106 Ritalin and 10 Focalin cases retrieved for mania cumulatively. With potential mechanism and listedness, the strength of evidence is considered strong.
Risk factors and risk groups	Risk factors include family history, perinatal complications, early parental separation, institutionalization, poor family function, other medications (e.g. steroids, anticholinergic drugs), illegal drugs, abuse, and alcohol dependence. Patients exhibiting emotional liability, social anxiety, social withdrawal, passivity, poor peer relations, and disruptive and aggressive behavior may also be at risk.

Risk minimization measures	**Routine risk minimization measure** SmPC: Posology/Admin (Section 4.2) SmPC: Contraindications (Section 4.3) SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-7 Important identified risk: Verbal and Motoric tics (including Tics, Tourette's syndrome, dystonia and repetitive behaviors)

Evidence for linking the risk to the medicine	**Verbal and motoric tics** Current evidence is based on 862 Ritalin cases and 156 Focalin cases retrieved cumulatively with known potential mechanism and listedness; the strength of evidence is considered strong. **Repetitive behaviours** Current evidence is based on 133 Ritalin and 22 Focalin cases retrieved cumulatively with no strong evidence for mechanism of action in humans and unlistedness (listed under additional adverse reactions reported with other methylphenidate containing products). The strength of evidence is considered weak. The reporting rate of Verbal and motoric tics as of 31-Oct-2021: Ritalin 78.84 cases/million PTY; Focalin 34.16 cases/million PTY.
Risk factors and risk groups	**Verbal and motoric tics** Tourette's syndrome, tics and dystonias – familial occurrence, previous head trauma, environmental factors. **Repetitive behaviours** Factors believed to be positively associated with this condition include: being female, black, not working for pay, a history of alcohol consumption, affective or phobic disorders, and undesirable life events.
Risk minimization measures	**Routine risk minimization measure** SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) except dystonias **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-8 Important identified risk: Depression

Evidence for linking the risk to the medicine	Current evidence is based on 1277 Ritalin and 99 Focalin cases, and 9 both Ritalin as well as Focalin retrieved cumulatively. Based on the unclear mechanism of action and unlistedness, the strength of evidence is considered as weak. The reporting rate of depression as of 31-Oct-2021: Ritalin 101.65 cases/million PTY; Focalin 20.54 cases/million PTY.
Risk factors and risk groups	Risk factors for depression include: predisposing genetic factors, gender, environmental stressors, poor social support, childhood sexual abuse, other psychiatric illness, substance abuse and trauma.
Risk minimization measures	**Routine risk minimization measure** SmPC: Contraindications (Section 4.3) SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-9 Important identified risk: Aggression

Evidence for linking the risk to the medicine	**Aggression** Current evidence is based on 1368 Ritalin, 168 Focalin cases, and 11 both Ritalin as well as Focalin retrieved cumulatively. Considering the unclear mechanism of action and unlistedness, the strength of evidence is considered as weak. The reporting rate for Aggression as of 31-Oct-2021: Ritalin 109.27 cases/million PTY; Focalin 34.35 cases/million PTY.
Risk factors and risk groups	**Aggression** ADHD may have associated features which can be categorized as aggressive behavior. Such features or behaviors may include temper outbursts, low frustration tolerance, bossiness, stubbornness, antagonistic relationships, blurting out inappropriate comments, grabbing objects from others and other troublesome impulsive behaviors. In the review of the cumulative data, it was noted that several of the reported cases could be attributed to the underlying condition of ADHD, its associated psychiatric co-morbidities, listed AEs such as psychotic reactions, and concomitant medications. It is possible that co-morbid pre-existing psychiatric diagnoses may have gone unrecognized and were not included in the case reports. **Hostility** Risk factors include: sex (male gender), lower education, race (blacks) and age (the young). ADHD may have associated features which can be categorized as hostile behavior.

Risk minimization measures	**Routine risk minimization measure** SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) except hostility and dystonia **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-10 Important identified risk: Drug abuse and drug dependence

Evidence for linking the risk to the medicine	**Drug abuse and drug dependence** Current evidence is based on 2068 Ritalin cases and 103 Focalin cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered weak. **Diversion** Current evidence is based on11 Ritalin cases and 5 Focalin cases retrieved cumulatively. The strength of evidence is considered weak.
Risk factors and risk groups	**Drug abuse and drug dependence** Risk factors for drug abuse and dependence include: drug availability, peer pressure, cultural factors, governmental policies, genetic disposition, personality disorder, family disruption and dependence problems, social deprivation, depression and suicidal behavior. ADHD is a risk factor for drug abuse and drug dependence. Late initiation of stimulant medication prescription (i.e. secondary school age vs. elementary school age) is associated with a higher risk of drug abuse. **Diversion** In adult patients, the risk of MPH diversion is associated with age of first prescription (younger) and MPH misuse.
Risk minimization measures	SmPC: Posology/Admin (Section 4.2) SmPC: Warning (Section 4.4) SmPC: Undesirable effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-11 Important identified risk: Decreased rate of growth

Evidence for linking the risk to the medicine	**Decreased rate of growth** Current evidence is based on 164 Ritalin cases and 21 Focalin cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered strong. The reporting rate of Decreased rate of growth as of 31 Oct 2021: Ritalin 13.00 cases/million PTY and Focalin 4.03 cases/million PTY.
Risk factors and risk groups	**Decreased rate of growth** Not known. **Effects on Final height** Risk factors include: hormonal imbalances, nutrition, infection, psychosocial stress, food contaminants, pollutants and chondrodysplasia, zinc and protein deficiency
Risk minimization measures	**Routine risk minimization measure** SmPC: Posology/Admin (Section 4.2) SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-12 Important identified risk: Reduced weight gain

Evidence for linking the risk to the medicine	Current evidence is based on 2630 Ritalin cases, 241 Focalin cases, and 15 both Ritalin as well as Focalin retrieved cumulatively with potential mechanism and listedness. The strength of evidence is considered strong.
Risk factors and risk groups	Hormonal imbalances, nutrition, infection, psychosocial stress, food contaminants, pollutants and chondrodysplasia, zinc and protein deficiency
Risk minimization measures	**Routine risk minimization measure** SmPC: Posology/Admin (Section 4.2) SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-13 Important identified risk: Cerebrovascular disorders

Evidence for linking the risk to the medicine	Current evidence is based on 147 Ritalin cases and 11 Focalin cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered strong. The reporting rate of Cerebrovascular disorders as of 31-Oct-2021 was 11.65 cases/million PTY for Ritalin and 2.11 cases/million PTY for Focalin.
Risk factors and risk groups	Known risk factors for cerebrovascular disorders include smoking, hypertension, obesity, dyslipidemia, diabetes mellitus, and vascular disorders.
Risk minimization measures	**Routine risk minimization measure** SmPC: Contraindications (Section 4.3) SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-14 Important identified risk: Neonatal toxicity

Evidence for linking the risk to the medicine	**Neonatal cardio-respiratory toxicity** Current evidence is based on 6 Ritalin cases (and no Focalin cases) retrieved cumulatively with potential mechanism the strength of evidence is considered weak. **Effects on neonatal growth** Current evidence is based on 1 Ritalin case retrieved cumulatively with potential mechanism and unlistedness, the strength of evidence is considered weak. **Cardiac malformations** Current evidence is based on 3 Ritalin cases retrieved cumulatively for unknown Ritalin formulation which had several risk factors and confounders; thus, causality cannot be fully established. Overall, the strength of evidence is considered low.
Risk factors and risk groups	Risk factors include drug/alcohol abuse, complications of pregnancy.
Risk minimization measures	**Routine risk minimization measure** SmPC: Warning (Section 4.6) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-15 Important identified risk: Seizures

Evidence for linking the risk to the medicine	Current evidence is based on literature and post-marketing reports. The reporting rate of Seizures as of 31-Oct-2021: Ritalin 37.00 cases/million PTY; Focalin 12.28 cases/million PTY. Taking all evidence in consideration, a causal association is not established.
Risk factors and risk groups	The most common cause of seizures is epilepsy. But not every person who has a seizure has epilepsy. Sometimes seizures happen because of: • High fever, which can be associated with an infection such as Meningitis. • Lack of sleep. • Low blood sodium (hyponatremia), which can happen with diuretic therapy • Medications, such as certain pain relievers, antidepressants or smoking cessation therapies, that lower the seizure threshold • Head trauma that causes an area of bleeding in the brain • Stroke • Brain tumor • Illegal or recreational drugs, such as amphetamines or cocaine • Alcohol abuse, during times of withdrawal or extreme intoxication
Risk minimization measures	**Routine risk minimization measure** SmPC: Section 4.4 **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-16 Important identified risk: Withdrawal syndrome

Evidence for linking the risk to the medicine	Current evidence is based on 379 Ritalin cases and 29 Focalin cases retrieved cumulatively with potential mechanism the strength of evidence is considered weak. The reporting rate of Withdrawal syndrome as of 31-Oct-2021: Ritalin 30.03 cases/million PTY; Focalin 5.57 cases/million PTY
Risk factors and risk groups	Not known.
Risk minimization measures	**Routine risk minimization measure** SmPC: Warning (Section 4.4) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-17 Important potential risk: Sexual maturation (delayed)

Evidence for linking the risk to the medicine	Current evidence is based on 12 Ritalin cases (and no Focalin cases) received cumulatively, and as the event is unlisted, the strength of evidence is considered weak.
Risk factors and risk groups	Not well established. Disorders including diabetes mellitus, inflammatory bowel disease, kidney disease, cystic fibrosis and anemia can delay sexual development. Development may be delayed in adolescents receiving radiation- or chemotherapy or who lose body weight.
Risk minimization measures	**Routine risk minimization measure** None **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

Table 13-18 Important potential risk: Suicidality

Evidence for linking the risk to the medicine	Current evidence is based on 485 Ritalin and 49 Focalin cases retrieved cumulatively, with known potential mechanism and information provided in SmPC, the strength of evidence is considered strong. The reporting rate of Suicidality as of 31-Oct-2021: Ritalin 38.43 cases/million PTY; Focalin 9.40 cases/million PTY.
Risk factors and risk groups	There may be an association between ADHD and suicide, mostly through increasing severity of co-morbid conditions.
Risk minimization measures	**Routine risk minimization measure** SmPC: Contraindication (Section 4.3) SmPC: Warning (Section 4.4) SmPC: Undesirable Effects (Section 4.8) **Additional risk minimization measures** None
Additional pharmacovigilance activities	None

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 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 Ritalin.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Ritalin.