

## **Summary of the risk management plan for Ritalin/Ritalin SR/Ritalin LA (methylphenidate)**

This is a summary of the risk management plan (RMP) for Ritalin/Ritalin SR/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.

### **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, Ritalin SR and Ritalin LA) and narcolepsy (Ritalin and Ritalin SR). It is also indicated in ADHD in adults (Ritalin LA only). It contains Methylphenidate and is given by oral route to patients in tablet (10 mg), SR tablet (20 mg) and LA capsule form (10mg, 20 mg, 30 mg, 40 mg, and 60 mg).

### **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 the case of Ritalin, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

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

#### **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).

**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* Cerebrovascular disorders Neonatal toxicity**
Important potential risks	Sexual maturation (delayed)* Suicidality Withdrawal syndrome
Missing information	Long-term effects
* only relevant for pediatric populations	
** only relevant for adult populations	

**II B: Summary of important risks**

**Table 1      Important identified risk: Serious cardiovascular events: Arrhythmias**

Evidence for linking the risk to the medicine	Current evidence is based on 336 Ritalin (258 serious and 78 non-serious cases) and 33 Focalin (30 serious and three non- serious) cases retrieved cumulatively 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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 2      Important identified risk: Serious cardiovascular events: Arrhythmias (tachycardia)**

Evidence for linking the risk to the medicine	Current evidence is based on 896 Ritalin (432 serious and 464 non-serious cases) and 90 Focalin (54 serious, 36 non- serious cases) cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered strong.
Risk factors and risk groups	Known risk factors for tachycardia include: family history of heart disease, congenital heart disorders, cigarette smoking, coronary artery disease, heart attack, diabetes, high cholesterol, high blood pressure, drug/alcohol abuse, excess weight, high-fat diet, sedentary lifestyle, stress.
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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 3      Important identified risk: Serious cardiovascular events: Sudden death**

Evidence for linking the risk to the medicine	Current evidence is based on 37 Ritalin (all serious) and a single Focalin case (serious) retrieved cumulatively with no strong evidence for mechanism of action the strength of evidence is considered weak.
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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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 4      Important identified risk: Serious cardiovascular events: Ischemic cardiac events**

Evidence for linking the risk to the medicine	Current evidence is based on 231 Ritalin (182 serious and 49 non-serious cases) and eight Focalin (seven serious and one non-serious) cases retrieved cumulatively with no strong evidence for mechanism of action and unlistedness, the strength of evidence is considered weak
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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 5 Important identified risk: Serious cardiovascular events: Cardiomyopathy**

Evidence for linking the risk to the medicine	Current evidence is based on 36 Ritalin (34 serious and two non-serious) cases and one serious Focalin case retrieved cumulatively with potential mechanism the strength of evidence is considered weak.
Risk factors and risk groups	<ul style="list-style-type: none"> <li>•A family history of cardiomyopathy, heart failure, or sudden cardiac arrest (SCA)</li> <li>•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</li> <li>•Diabetes or other metabolic diseases, or severe obesity</li> <li>•Diseases that can damage the heart, such as hemochromatosis, sarcoidosis, or amyloidosis</li> <li>•Long-term alcoholism</li> <li>•Long-term high blood pressure</li> </ul> <p>Primarily due to genetic defects or secondarily as a consequence of multiple factors (infections, toxins, alcohol, drugs, metals, autoimmune, etc).</p>
Risk minimization measures	<p>Routine risk minimization measure none</p> <p>Additional risk minimization measures none</p>
Additional pharmacovigilance activities	None

**Table 6 Important identified risk: Psychosis/mania**

Evidence for linking the risk to the medicine	Current evidence is based on 2,376 Ritalin (1,058 serious and 1,318 non-serious cases) and 382 Focalin (112 serious, 270 non-serious cases) cases retrieved 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	<p>Routine risk minimization measure SmPC: Posology/Admin (Section 4.2)</p>

	<p>SmPC: Contraindications (Section 4.3)</p> <p>SmPC: Warnings (Section 4.4)</p> <p>SmPC Undesirable Effects (Section 4.8)</p> <p>Additional risk minimization measures</p> <p>Physicians' educational materials provided through a MPH website</p>
Additional pharmacovigilance activities	None

**Table 7 Important identified risk: Verbal and motoric tics**

Evidence for linking the risk to the medicine	<p><b>Verbal and motoric tics</b></p> <p>Current evidence is based on 651 Ritalin (195 serious and 456 non-serious cases) and 105 Focalin (28 serious, 77 non- serious cases) cases retrieved cumulatively with known potential mechanism and listedness, the strength of evidence is considered strong.</p> <p><b>Repetitive behaviours</b></p> <p>Current evidence is based on 153 Ritalin (64 serious and 89 non-serious cases) and 21 Focalin (seven serious and 14 non- serious) 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), potential mechanism and as the event is unlistedness, the strength of evidence is considered weak.</p>
Risk factors and risk groups	<p><b>Verbal and motoric tics</b></p> <p>Tourette's syndrome, tics and dystonias – familial occurrence, previous head trauma, environmental factors.</p> <p><b>Repetitive behaviours</b></p> <p>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.</p>
Risk minimization measures	<p>Routine risk minimization measure</p> <p>SmPC: Warnings (Section 4.4)</p> <p>SmPC: Undesirable Effects (Section 4.8) except dystonias</p> <p>Additional risk minimization measures</p> <p>Physicians' educational materials provided through a MPH website</p>

Additional pharmacovigilance activities	None
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**Table 8      Important identified risk: Depression**

Evidence for linking the risk to the medicine	Current evidence is based on 1097 Ritalin (522 serious and 575 non-serious cases) and 441 Focalin (101 serious, 340 non-serious cases) cases retrieved cumulatively. Based on the unclear mechanism of action and unlistedness, the strength of evidence is considered as weak.
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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 9      Important identified risk: Aggression**

Evidence for linking the risk to the medicine	<b>Aggression</b> Current evidence is based on 1184 Ritalin (345 serious and 839 non-serious cases) and 162 Focalin (41 serious, 121 non-serious cases) cases retrieved cumulatively. The unclear mechanism of action and unlistedness, the strength of evidence is considered as weak. <b>Hostility</b> Current evidence is based on six Ritalin (three serious and three non-serious cases) and four Focalin (two serious and two non-serious cases) cases retrieved cumulatively with unknown potential mechanism and as event is unlisted, strength of evidence is considered weak
Risk factors and risk groups	<b>Aggression</b>

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 Physicians’ educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 10      Important identified risk: Drug abuse and drug dependence**

Evidence for linking the risk to the medicine	<b>Drug abuse and drug dependence</b> Current evidence is based on 1640 Ritalin (1196 serious and 444 non-serious) cases and 92 Focalin (60 serious and 32 non-serious) cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered weak. <b>Diversion</b> Current evidence is based on nine Ritalin (five serious and four non-serious) cases and five non-serious Focalin cases retrieved cumulatively with potential mechanism and unlistedness, the strength of evidence is considered weak.
Risk factors and risk groups	<b>Drug abuse and drug dependence</b>

	<p>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.</p> <p>Late initiation of stimulant medication prescription (i.e. secondary school age vs. elementary school age) is associated with a higher risk of drug abuse.</p> <p><b>Diversion</b></p> <p>In adult patients, the risk of MPH diversion is associated with age of first prescription (younger) and MPH misuse.</p>
Risk minimization measures	<p>SmPC: Posology/Admin (Section 4.2)</p> <p>SmPC: Warning (Section 4.4)</p> <p>SmPC: Undesirable effects (Section 4.8)</p> <p>Additional risk minimization measures</p> <p>Physicians' educational materials provided through a MPH website</p>
Additional pharmacovigilance activities	None

**Table 11      Important identified risk: Decreased rate of growth**

Evidence for linking the risk to the medicine	<p><b>Decreased rate of growth</b></p> <p>Current evidence is based on 152 Ritalin (95 serious and 57 non-serious cases) and 19 Focalin (9 serious, 10 non-serious cases) cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered strong.</p> <p><b>Effects on Final height</b></p> <p>Current evidence is based on 11 Ritalin (three serious and eight non-serious cases) and one Focalin case (non-serious case) retrieved cumulatively with potential mechanism and as the event is unlisted, the strength of evidence is considered weak.</p>
Risk factors and risk groups	<p><b>Decreased rate of growth</b></p> <p>Not known.</p> <p><b>Effects on Final height</b></p> <p>Risk factor include: hormonal imbalances, nutrition, infection, psychosocial stress, food contaminants, pollutants and chondrodysplasia, zinc and protein deficiency</p>
Risk minimization measures	<p>Routine risk minimization measure</p> <p>SmPC: Posology/Admin (Section 4.2)</p>

	SmPC: Warnings (Section 4.4) SmPC: Undesirable Effects (Section 4.8) Additional risk minimization measures Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 12      Important identified risk: Cerebrovascular disorders**

Evidence for linking the risk to the medicine	Current evidence is based on 126 Ritalin (125 serious and one non-serious case) and 11 Focalin (10 serious, 1 non-serious cases) cases retrieved cumulatively with potential mechanism and listedness, the strength of evidence is considered strong.
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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 0      Important identified risk: Neonatal toxicity**

Evidence for linking the risk to the medicine	<b>Neonatal cardio-respiratory toxicity</b> Current evidence is based on eight Ritalin (eight serious and zero non-serious) cases and zero Focalin serious case retrieved cumulatively with potential mechanism the strength of evidence is considered weak. <b>Effects on neonatal growth</b> Current evidence is based on one serious Ritalin case retrieved cumulatively with potential mechanism and unlistedness, the strength of evidence is considered weak.
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 14      Important potential risk: Sexual maturation (delayed)**

Evidence for linking the risk to the medicine	Current evidence is based on 12 Ritalin (five serious and seven non-serious cases) and no cases received for Focalin 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 15      Important potential risk: Suicidality**

Evidence for linking the risk to the medicine	Current evidence is based on 464 Ritalin (419 serious and 45 non-serious cases) and 50 Focalin (43 serious and seven non-serious cases) cases retrieved cumulatively, with known potential mechanism and information provided in SmPC, the strength of evidence is considered strong.
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 Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**Table 16      Important potential risk: Withdrawal syndrome**

Evidence for linking the risk to the medicine	Current evidence is based on 309 Ritalin (173 serious and 136 non-serious) cases and 19 Focalin (13 serious and six non-serious) cases retrieved cumulatively with potential mechanism the strength of evidence is considered weak.
Risk factors and risk groups	Not known.
Risk minimization measures	Routine risk minimization measure SmPC: Warning (Section 4.4) Additional risk minimization measures Physicians' educational materials provided through a MPH website
Additional pharmacovigilance activities	None

**II C: Post-authorization 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 Ritalin.

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

There are no studies required for Ritalin.