LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metylfenidat Amdipharm
(methylphenidate hydrochloride)

SE/H/2106/01-03/DC

This module reflects the scientific discussion for the approval of Metylfenidat Amdipharm. The procedure was finalised on 2021-09-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Metylfenidat Amdipharm,10 mg, 20 mg, 30 mg, modified-release capsule, hard.

The active substance is methylphenidate hydrochloride. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Metylfenidat Amdipharm, 10 mg, 20 mg, 30 mg, modified-release capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Amdipharm Ltd., Ireland, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and UK(NI) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Equasym Depot, 10 mg, 20 mg or 30 mg, modified-release capsule, hard, authorised in Sweden since 2007, with Shire Pharmaceuticals Ireland Limited as marketing authorisation holder.

The reference product used in the bioequivalence studies is Equasym Retard, 30 mg, modified-release capsule, hard from Germany with Shire Pharmaceuticals Ireland Limited as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS UK(NI): Equasym Depot, 10 mg, 20 mg or 30 mg, modified-release capsule, hard, authorised in Sweden since 2007, with Shire Pharmaceuticals Ireland Limited as marketing authorisation holder.
The justification to use this product is based on information received from UK(NI) and on RMS's own files. The ERP information was circulated by RMS during validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of methylphenidate are well known. As methylphenidate is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Metylfenidat Amdipharm is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Metylfenidat Amdipharm from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted two single dose bioequivalence studies comparing Methylphenidate HCl with the reference product Equasym. The bioequivalence studies were performed at the 30 mg strength, one in fasting and one in fed condition, respectively.

Pharmacokinetic properties

Absorption: Methylphenidate is readily absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism with an oral bioavailability of approximately 30% (11-51%). The modified release formulation has a plasma profile showing two phases of active substance release, with a sharp, initial, upward slope similar to a methylphenidate immediate-release tablet, and a second rising portion approximately three hours later, followed by a gradual decline.

Following oral administration of methylphenidate modified release capsule, hard, peak plasma concentrations occur approximately 1-2 hours after administration of 0.30 mg/kg. The peak plasma concentrations that derive from the immediate release component (30% of dose), show considerable intersubject variability. The methylphenidate contained in the modified-release component (70% of dose) is gradually released over the next several hours resulting in a second maximum observed concentration in most subjects at 4.5 hours after dosing following a gradual decrease of methylphenidate plasma levels.

No significant drug accumulation is expected for methylphenidate based on studies with other modified release formulations following single and repeated once daily dosing.

Ingestion together with food with a high fat content delays its absorption (T_{max}) by approximately one hour and increases the maximum concentration (C_{max}) by approximately 30% and the amount absorbed (AUC) by approximately 17%. Administration is recommended before breakfast.

Linearity: The area under the plasma concentration curve (AUC), as well as the peak plasma concentration, is proportional to the dose.

Elimination: Methylphenidate is eliminated from the plasma with a mean half-life of 2 hours.

Study 339B17

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Methylphenidate HCl, 30 mg, modified release capsule with Equasym, 30 mg, modified release capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of methylphenidate were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{\text{phase 1}}$, $AUC_{\text{phase 2}}$, $C_{max,\text{ phase 1}}$ and $C_{max,\text{ phase 2}}$. The clinical part of the study was conducted between 8 November 2018 and 22 November 2018 and the analytical part of the study was conducted between 4 December 2018 and 14 December 2018.

Results

The results from the pharmacokinetic and statistical analysis are presented in table 1.

Table 1: Pharmacokinetic parameters of methylphenidate after single 30 mg dose of the test and reference products in the fasted state (arithmetic mean of non-transformed values ± SD, T/R ratios, 90 % CI and intra-subject CV %, n= 24.

PK Metric	Test	Reference	Ratio* T/R	90% CI, lower, upper	Intra-subject CV** (%)
AUC_{0-t} (ng/ml*h)	75.9±25.9	73.6±25.9	103.3	100.3, 106.4	5.9
$AUC_{0-\infty}$ (ng/ml*h)	81.6±26.8	79.4±29.1	103.2	100.4, 106.2	5.8
$AUC_{t-\infty}$ (%)	7.1±3.2	7.1±2.7	-	-	-
AUC_{phase1} (ng/ml*h)	4.3±2.0	4.3±2.2	102.0	85.0, 122.4	38.0
AUC_{phase2} (ng/ml*h)	71.7±24.5	69.2±24.3	103.5	100.2, 106.9	6.5
$C_{max,phase1}$ (ng/ml)	5.7±2.0	6.0±2.7	98.7	86.7, 112.3	26.5
$C_{max,phase2}$ (ng/ml)	8.4±3.1	7.6±2.4	109.9	104.0, 116.2	11.3
$t_{max,phase1}$ (h) ***	1.25 (0.75, 1.50)	1.50 (0.75,1.50)	-	-	-
$t_{max,phase2}$ (h) ***	4.5 (3.5, 6.0)	4.5 (1.5, 5.5)	-	-	-
$t_{1/2}$ (h)	5.8 (±1.3)	5.8 (±1.2)	-	-	-

* log-transformed values, geometric mean ratios, ** residual CV, *** median (range)

The cut-off time point between absorption phase 1 and phase 2 was defined as median $t_{min,between}$ of the reference product and was determined as 1.50 hours after drug administration.

For AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{phase\ 1}$, $AUC_{phase\ 2}$, $C_{max,\ phase\ 1}$ and $C_{max,\ phase\ 2}$. the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for methylphenidate.

Study 346B17

Methods

This was a single-dose, two-treatment, four-period, two-sequence, crossover study conducted in 24 healthy volunteers, comparing Methylphenidate HCl, 30 mg, modified release capsule with Equasym, 30 mg, modified release capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of methylphenidate were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{phase\ 1}$, $AUC_{phase\ 2}$, $C_{max,\ phase\ 1}$ and $C_{max,\ phase\ 2}$. The clinical part of the study was conducted between 29 March 2018 and 11 May 2018 and the analytical part of the study was conducted between 27 April 2018 and 16 May 2018.

Table 2: Pharmacokinetic parameters of methylphenidate after replicate single 30 mg doses of the test and reference products in fed state (arithmetic mean of non-transformed values ± SD, T/R ratios, 90% CI and intra-subject CV%, n=48; 346B17)

PK Metric	Test	Reference	Ratio* T/R	90% CI, lower, upper	Intra-subject CV** (%)
AUC_{0-t} (ng/ml*h)	89.5±20.7	86.2±19.3	103.6	100.9, 106.4	7.8
$AUC_{0-\infty}$ (ng/ml*h)	93.8±22.2	92.1±20.9	101.7	99.2, 104.2	7.2
$AUC_{t-\infty}$ (%)	4.5±1.9	6.2±3.2	-	-	-
AUC_{phase1} (ng/ml*h)	7.0±3.5	7.6±3.5	93.1	78.5,110.5****	53.5
AUC_{phase2} (ng/ml*h)	82.5±19.3	78.9±18.2	104.4	101.5, 107.4	8.4
$C_{max,phase1}$ (ng/ml)	6.1±2.4	6.6±2.5	89.7	80.5, 99.9	32.5
$C_{max,phase2}$ (ng/ml)	11.3±2.6	9.7±2.9	118.0	112.0, 124.3	15.4
$t_{max,phase1}$ (h) ***	2.6 (1.0, 2.6)	2.6 (0.8 2.6)	-	-	-
$t_{max,phase2}$ (h) ***	5.0 (3.5, 7.5)	5.0 (2.6, 6.5)	-	-	-
$t_{1/2}$ (h)	4.9±1.0	5.3±1.1	-	-	-
$t_{min,between}$ (h)	-	2.6 (1.3, 4.0)	-	-	-

* log-transformed values, geometric mean ratios, ** residual CV, *** median (range), **** the acceptance range for AUC_{phase1} can be widened to 69.84 – 143.19 % as CV(%) >50 after replicate REF.

For AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{phase\ 2}$, $C_{max,\ phase\ 1}$ and $C_{max,\ phase\ 2}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for methylphenidate.

The cut-off time point between absorption phase 1 and phase 2 was defined as median $t_{min,between}$ of the reference product and was determined as 2.625 hours after drug administration.

For the AUC_{phase1}, the intra-subject variability after replicate administration of the reference products was 53.52% thereby enabling to widen the bioequivalence acceptance margins by use of the scaled average bioequivalence approach for highly variable drugs in line with the bioequivalence guideline recommendations up to 69.84 - 143.19%.

A biowaiver was sought for the additional strengths of 10 and 20 mg.

Discussion and overall conclusion

The bioequivalence studies 339B17 (fasting) and 346B17 (fed) were conducted in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1 /Corr) and Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1). The bioanalytical methods were adequately validated.

The results of study 339B17 and study 346B17 with the 30 mg formulation can be extrapolated to the other strengths 10 mg and 20 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1, section 4.1.6.

Based on the submitted bioequivalence studies, Metylfenidat Amdipharm is considered bioequivalent with Equasym.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted a revised risk management plan (version 0.2, DLP 31 July 2020, signed 10 February 2021), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Metylfenidat Amdipharm.

In this revised version, *neonatal toxicity* was removed as a risk (as was requested), given that this risk should only be included for products with an indication for adult patients.

Safety specification

Summary of safety concerns	
Important identified risks	• Serious cardiovascular events • Psychosis/Mania • Verbal or motoric tics • Depression • Aggression • Drug abuse/Drug dependence • Withdrawal syndrome • Reduced weight gain • Decreased rate of growth • Seizures • Cerebrovascular Disorders
Important potential risks	• Suicidality • Sexual Maturation delayed
Missing information	• Long-term effects

The safety specification follows that of the reference product and is considered acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Serious cardiovascular events	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4, 4.8 • PIL sections 2, 4 Section 4.3 of the SmPC states that the use of methylphenidate is contraindicated in patients with pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina pectoris, hemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels). SmPC Section 4.4 advises that the Patients who are being considered for treatment with stimulant medications should have a careful	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** Not Proposed

	history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate. Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose, and then at least every 6 months. Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Stimulant products are not recommended in patients with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine. Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events. Section 4.8 of the SmPC mentions cardiovascular disorders such as arrhythmia, tachycardia, palpitations at common frequency, chest pain at uncommon frequency, angina pectoris at rare frequency, cardiac arrest and myocardial infarction at very rare frequency and supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles at not known frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:**	

	Physician educational tools: • 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	
Psychosis/Mania	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 • PIL sections 2, 4 Section 4.4 of the SmPC states that the patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring for worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate. Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse. Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in patients without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate. Section 4.5 of the SmPC advises to abstain from alcohol during methylphenidate treatment. As alcohol may exacerbate the adverse CNS effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** Not Proposed

	of psychoactive medicinal products, including methylphenidate. Section 4.8 of the SmPC states insomnia and nervousness at very common frequency, anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour and bruxism at common frequency, Psychotic disorders, auditory, visual and tactile hallucinations, anger, suicidal ideation, mood altered, mood swings, restlessness, tearfulness, tics or worsening of pre-existing tics of Tourette's syndrome, hypervigilance and sleep disorder at uncommon frequency, mania, disorientation, libido disorder, Suicidal attempt (including completed suicide), transient depressed mood, abnormal thinking, apathy, repetitive behaviour, over-focussing, and delusions, thought disturbances, confusional state, dependence, and logorrhoea at not known frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	
Verbal or motoric tics	**Routine risk minimisation measures:** • SmPC section 4.4 • PIL sections 2 Section 4.4 states that the patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring for worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration. Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

	reported. Family history should be assessed and clinical evaluation of the patients for tics or Tourette's syndrome should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate. Monitoring should be at every adjustment of dose and then at least every 6 months or every visit. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	
Depression	**Routine risk minimisation measures:** • SmPC section 4.3, 4.4, 4.8 • PIL sections 2, 4 SmPC Section 4.3 reports methylphenidate is contraindicated in diagnosis or history of severe depression. SmPC Section 4.4 states that the patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring for development of de novo or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor include depression. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Close ongoing monitoring is essential in these patients. Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

	Careful supervision is required during withdrawal from abusive use since severe depression may occur. SmPC Section 4.8 mentions depression at common frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	
Aggression	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8 • PIL sections 2, 4 SmPC section 4.4 states that 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 behavior 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 behavior changes bearing in mind that upwards or downwards titration may be appropriate. Treatment interruption can be considered. SmPC Section 4.8 reports aggression with common frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

Drug abuse/Drug dependence	**Routine risk minimisation measures:** • SmPC section 4.2, 4.4, 4.8 • PIL sections 2, 3 SmPC section 4.2 states that the patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate. SmPC section 4.4 states that methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion. Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially in response to parenteral abuse. 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 dose on their own initiative. For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered. SmPC section 4.8 mentions cases of abuse and dependence have been described, more often with immediate-release formulations. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Withdrawal syndrome	**Routine risk minimisation measures:** • SmPC section 4.4 Section 4.4 of the SmPC states that the patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according. Psychiatric disorders to monitor for withdrawal.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:**

	A careful supervision during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up and during withdrawal from abusive use since severe depression may occur. Careful supervision is required during withdrawal from abusive use since severe depression may occur. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	None proposed
Reduced weight gain	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8 • PIL sections 4 SmPC Section 4.4 states that the growth should be monitored during methylphenidate treatment: Height, weight and appetite should be recorded at least 6-monthly with maintenance of a growth chart. Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. SmPC section 4.8 mention moderately reduced weight with methylphenidate at common frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

	• Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy • Chart for ongoing monitoring during methylphenidate treatment	
Decreased rate of growth	**Routine risk minimisation measures:** • SmPC section 4.3, 4.4, 4.8 • PIL sections 4 SmPC Section 4.3 and 4.4 states that the growth should be continuously monitored during methylphenidate treatment: Height, weight and appetite should be recorded at least 6-monthly with maintenance of a growth chart. Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted. SmPC section 4.8 mentions growth retardation during prolonged of methylphenidate use in children at a common frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Seizures	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8 • PIL sections 2, 4 SmPC section 4.4 states caution for Methylphenidate use in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patient with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

	abnormalities. If seizure frequency increases or new onset seizures occur, methylphenidate should be discontinued SmPC section 4.8 mentions convulsions at a very rare frequency and grand mal convulsions at not known frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing	
Cerebrovascular disorder	**Routine risk minimisation measures:** • SmPC section 4.3, 4.4, 4.5, 4.8 • PIL sections 2, 4 SmPC section 4.3 and 4.4 states, methylphenidate is contraindicated in patients with pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate. SmPC section 4.5 states, Caution is advised in patients being treated with methylphenidate with any other active substances that can also elevate blood pressure. SmPC Section 4.8 mentions Cerebrovascular disorders* (including vasculitis, cerebral haemorrhage, cerebral arteritis, cerebral occlusion and cerebrovascular accidents) with methylphenidate at unknown frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

	• Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	
Important potential risks		
Suicidality	**Routine risk minimisation measures:** • SmPC section 4.3, 4.4, 4.8 • PIL sections 2, 4 SmPC section 4.3 states that Methylphenidate is contraindicated in patients with diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder. SmPC section 4.4 states that the patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary, and consideration should be given to a possible discontinuation of methylphenidate. SmPC section 4.8 mentions Psychotic disorders and suicidal ideation at the uncommon frequency and Suicidal attempt [including completed suicide] at very rare frequency. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Physician educational tools: • Physician's guide to prescribing • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Sexual Maturation delayed	**Routine risk minimisation measures:** • SmPC section 4.4	**Routine pharmacovigilance activities beyond adverse**

	SmPC section 4.4 states that the Methylphenidate treatment is not indicated in all patients with ADHD and the decision to use the medicinal product must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring for growth of the children. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Not Proposed	**reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Missing information		
Long-term effects	**Routine risk minimisation measures:** • SmPC section 4.4 • PIL sections 3 SmPC section 4.4 states that the methylphenidate does not need to be taken for ever. If you or your child takes Methylphenidate for more than a year, your doctor will stop treatment for a short time, e.g. during a school holiday. This will show if the medicine is still needed. **Legal Status:** Prescription only Medicine **Additional risk minimisation measures:** Not Proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

Summary of the RMP

The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.2, DLP 31 July 2020, signed 10 February 2021 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Metylfenidat Amdipharm, is found adequate. There are no objections to approval of Metylfenidat Amdipharm from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The benefit/risk ratio is considered positive and Metylfenidat Amdipharm, 10 mg, 20 mg, 30 mg, modified-release capsule, hard, is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Additional risk minimisation measures:

Physician educational tools:

- Physician's guide to prescribing
- Checklist 1: Methylphenidate checklist before prescribing
- Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy

VII. APPROVAL

The decentralised procedure for Metylfenidat Amdipharm,10 mg, 20 mg, 30 mg, modified-release capsule, hard, was positively finalised on 2021-09-22.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2106/01-04/IB/02	A Type IB variation application under change code C.I.11.a) to update the Risk Management Plan (RMP) for removal of additional risk minimization measures (ARMM's) based on PRAC's recommendation in the PSUSA procedure, PSUSA/00002024/202110. According to PRAC recommendation, following educational materials for healthcare professionals (aRMMs) have been removed from the RMP: - 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	No	2023-02-27	Approval	**Variation type IB no C.I.11.z:** To update the RMP and removal of additional risk minimization measures in line with the PSUSA procedure, PSUSA/00002024/202110). The following condition to the Marketing Authorisation has been lifted as a result of this variation application: The condition on educational material is lifted from the Marketing authorisation. **Additional risk minimisation measures - Educational material** **Physician educational tool:** Methylphenidate physician's guide to prescribing consisting of: • Introductory letter • Checklist 1: Methylphenidate checklist before prescribing • Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy • Chart for ongoing monitoring during methylphenidate treatment

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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