LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metylfenidat Amdipharm
(methylphenidate hydrochloride)

SE/H/2106/04/DC

This module reflects the scientific discussion for the approval of Metylfenidat Amdipharm. The procedure was finalised on 2022-09-27. 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, 40 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 is an extension, new strength, of the previously authorised product Metylfenidat Amdipharm, 10 mg, 20 mg, 30 mg, Modified-release capsule, hard, marketed by Amdipharm Limited since 2021.

The application for Metylfenidat Amdipharm, 40 mg, Modified-release capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Amdipharm Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and no concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Equasym Depot, 30mg, Modified-release capsule, hard, authorised in SE since 2007, with Takeda Pharmaceuticals International AG as marketing authorisation holder.

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

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

Pharmacology/Pharmacokinetics/Toxicology
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
The application is an extension (new strength 40 mg) of the previously authorised product: Metylfenidat Amdipharm, 10 mg, 20 mg, 30 mg, modified-release capsule, hard. The applied formulation is a multiple unit capsule formulation containing modified-release pellets.

The applicant applies for the strength 40 mg. Two bioequivalence studies with the 30 mg strength were submitted previously, one single dose study under fasting condition (study 339B17) and one single dose study in fed condition (study 346B17). Bioequivalence were demonstrated in both studies. No multiple dose study was performed which is acceptable as accumulation of methylphenidate was low as indicated by the single dose exposure results from the two studies (fasting and fed) where mean $AUC_{0\text{-}tau}$ covers more than 90% of $AUC_{0\text{-}\infty}$
From a pharmacokinetic point of view, it is sufficient to establish bioequivalence with only one strength as the AUC, as well as the peak plasma concentration, is proportional to the dose and the formulation belongs to the "multiple unit" type and all strengths contain identical pellets. For drugs with linear pharmacokinetics the bioequivalence study should in general be conducted at the highest strength, however in this case the bioequivalence studies were performed with the 30 mg strength which is considered acceptable since all strengths contain identical pellets and the only difference is the amount of pellets and size of the capsule.

Discussion and overall conclusion

The results of the two previously submitted single dose studies with the 30 mg formulation can be extrapolated to the applied strength 40 mg, according to conditions in the Guideline on the investigation of Bioequivalence; (CPMP/EWP/QWP/1401/98 Rev 1/Corr).

In conclusion, biowaiver for the strength 40 mg can be accepted.

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.

In modern treatment of ADHD, individualized dosing is of central importance. It is also important to enable over time fine adjustments of the dose, according to a range of factors, e.g. levels of physical activity, levels of work- or study load, status of comorbidities if any, co-medications if any, and so forth.
In a clinical perspective the proposed new 40 mg strength adds flexibility of clinical relevance, reduces the number of capsules to take at doses 40-60 mg. The maximum daily dose of methylphenidate is 60 mg.

The MAH has submitted a risk management plan, 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.

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 proposed safety concerns are the approved safety concerns as agreed in PSUSA PSUSA/00002024/201810 for methylphenidate.

Pharmacovigilance Plan

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

Risk minimisation measures
No additional risk minimisation activities than what are already in place, or changes to the RMP are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 2.0 signed 17-Mar-2022 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Addepta 10, 20 and 40 mg modified-release hard capsules (SE/H/2106/001-003/DC).

The bridging report submitted by the applicant has been found acceptable.

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. The bioequivalence results of two previously submitted single dose studies with the 30 mg formulation can be extrapolated to the applied strength 40 mg, and biowaiver for the strength 40 mg is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

Additional risk minimization measures as described in Section VIII.3 are implemented.

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: Metylphenidate checklist before prescribing
- Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy

The educational material should contain same key elements as for MAHs currently approved strengths of Metylfenidat Amdipharm (10 mg, 20 mg and 30 mg).

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

N/A

VII. APPROVAL

The decentralised procedure for Metylfenidat Amdipharm, 40 mg, Modified-release capsule, hard was positively finalised on 2022-09-27.

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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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