LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metylfenidat Medical Valley
(methylphenidate hydrochloride)

SE/H/1993/05/DC

This module reflects the scientific discussion for the approval of Metylfenidat Medical Valley. The procedure was finalised on 2024-11-28. 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 Medical Valley, 45 mg, Prolonged-release tablet.

The active substance is methylphenidate, 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 Medical Valley, 45 mg, prolonged-release tablet, is an extension, new strength, of the previously authorised product: Metylfenidat Medical Valley (SE/H/1993/01-04), 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablets. The application is submitted according to Art. 10(3) hybrid (new strength) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Concerta, 18 mg, prolonged release tablet (DE/H/6007/01) authorised in Sweden since 2002, with Janssen Cilag AB as marketing authorisation holder.

The reference product used in the bioequivalence studies is Concerta, 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablets, from Spain with Janssen Cilag AB as marketing authorisation holder.

Potential similarity with orphan medicinal products

N/A

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
This application is an extension (new strength, 45 mg) of the previously authorised product: Metylfenidat Medical Valley 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablet. The new strength is within the existing dose range of the reference product and bracketed by other approved strengths. No new non-clinical study was submitted in this application.

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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since this application is an extension (new strength, 45 mg) of the previously authorised product: Metylfenidat Medical Valley 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablet and the new strength is within the existing dose range of the reference 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 from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
This application is an extension (new strength, 45 mg) of the previously authorised product: Metylfenidat Medical Valley 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablet. The new strength is within the existing dose range of the reference product and bracketed by other approved strengths. No new bioequivalence study was submitted in this application.

The Approval of Metylfenidat Medical Valley, methylphenidate hydrochloride, 54/36/27/18 mg prolonged-release tablets was based on six bioequivalence studies between reference (Concerta) and Metylfenidat Medical Valley formulations. Single dose fasting study was performed on each strength, fed studies have been performed on the highest and lowest strength, multiple does study has been waived based on the AUCt/AUCinf ratio < 90% in the single dose studies.

These are:

- Single-dose study with **18 mg** strength under **fasted** conditions **(Study 0665-17)**
- Single-dose study with **18 mg** strength under **fed** conditions **(Study 0106-20)**
- Single-dose study with **27 mg** strength under **fasted** conditions **(Study 0104-20)**
- Single-dose study with **36 mg** strength under **fasted** conditions **(Study 0105-20)**
- Single-dose study with **54 mg** strength under **fasted** conditions **(Study 0715-16)**
- Single-dose study with **54 mg** strength under **fed** conditions **(Study 0714-16)**

Based on these previously assessed bioequivalence studies, Metylfenidat Medical Valley, 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablets is considered bioequivalent with Concerta, 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablets.

The absence of studies with the additional 45 mg strength is acceptable from a pharmacokinetic point of view as the pharmacokinetics of methylphenidate is linear between 18 and 54 mg. From a chemical-

pharmaceutical point of view the biowaiver is acceptable in accordance with the Guideline on the pharmacokinetic and clinical evaluation of modified release formulations, EMA/CHMP/EWP/280/96.

The results of the previously submitted studies performed with Metylfenidat Medical Valley 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablet can be extrapolated to the 45 mg strength according to conditions in the Guideline on the investigation of Bioequivalence; CHMP/QWP/EWP/1401/98 Rev. 1, section 4.1.6.

Pharmacokinetic properties of the active substance
Absorption: Methylphenidate is readily absorbed. Following oral administration of the originator Concerta to adults the drug overcoat dissolves, providing an initial maximum drug concentration at about 1 to 2 hours. The methylphenidate contained in the two internal drug layers is gradually released over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours, after which plasma levels of methylphenidate gradually decrease.

No differences in the pharmacokinetics of the originator Concerta were noted following single and repeated once daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once daily dosing are similar to those following the first dose of Concerta 18 mg.

The pharmacokinetics of the originator Concerta is not affected by food, and therefore the originator may be administered with or without food.

Linearity: Following administration of the originator Concerta in single doses of 18, 36, and 54 mg/day to adults, C_{max} and AUC_{inf} of methylphenidate were proportional to dose.

Elimination: Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of the originator Concerta was approximately 3.5 h.

Methylphenidate is a racemic mixture comprised of the d- and l- isomers. The d-isomer is more pharmacologically active than the l-isomer.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. This is an extension application for a new strength where a biowaiver applies. No additional clinical data is necessary.

Risk Management Plan
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 Medical Valley. The RMP version to be assessed as part of this application is RMP version 3.0, with data lock point 16-April-2024, signed 23-Apr-2024.

Part II Safety specification
Summary of safety concerns, RMP V 3.0 Metylfenidat Medical Valley 18, 27, 36, 45 and 54 mg depottabletter (methylphenidate):

Summary of safety concerns	
Important identified risks	• Serious cardiovascular events • Reduced weight gain (pediatric indication only) • Decreased rate of growth (pediatric indication only)

Important potential risks	• Sexual maturation delayed (pediatric indication only)
Missing information	• Long-term effects

This is in line with the latest safety specification of the reference product Concerta (RMP version 10.2 signed 26 April 2023), which is acceptable.

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

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 3.0, signed 23-Apr-2024 is considered acceptable. It has been updated in line with the reference product, and the only additions pertain to the new strength.

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 Methylphenidate hydrochloride, 18, 27, 36, 54 mg prolonged release tablets (SE/H/1909/001-004/DC,) for content and Phenichem 18, 27, 26 and 54 mg (SE/H/1912/01-04/DC) for layout.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Metylfenidat Medical Valley, 45 mg, Prolonged-release tablet 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

N/A

VII. APPROVAL

The decentralised procedure for Metylfenidat Medical Valley, 45 mg, Prolonged-release tablet was positively finalised on 2024-11-28.

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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

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

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