LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Methylphenidate Xiromed
(methylphenidate hydrochloride, methylphenidate)

Asp no: 2020-0576, 2020-0575

This module reflects the scientific discussion for the approval of Methylphenidate Xiromed. The procedure was finalised on 2021-01-26. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

The application for Methylphenidate Xiromed, 18 mg and 54 mg, prolonged-release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medical Valley Invest AB, applies through the Swedish National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Concerta, 18 mg and 54 mg, prolonged-release tablet authorised in UK (change of RMS to DE in 2018) since 2002, with Janssen Cilag as marketing authorisation holder.

The reference product used in the bioequivalence studies is Concerta, 18 mg and 54 mg, prolonged-release tablet from ES with Janssen Cilag as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation is granted under exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the application, the applicant has submitted three single dose bioequivalence studies. One bioequivalence study was performed at the 18 mg strength under fasting condition and two bioequivalence studies were performed at the 54 mg strength, one in fasting and fed condition respectively.

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.

Study 0665-17
Methods
This was a single-dose, two-way crossover study conducted in 68 healthy volunteers, comparing Methylphenidate, 18 mg, prolonged-release tablet with Concerta, 18 mg, prolonged-release tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of l-methylphenidate and d-methylphenidate were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $Cmax_{,0-3}$, $Cmax_{,3-24}$, AUC_{0-3}, AUC_{3-24}, AUC_{0-t} and $AUC_{0-\infty}$ for d-methylphenidate. The statistical analysis was based on the more active d-enantiomer which is found acceptable. The absorption of methylphenidate following administration of the test product is a little bit slower than the reference product in the first phase for d-methylphenidate based on the median t_{max} values (test:

1.667h and ref: 1.333h). However, the difference in t_{max} is assessed as small (20 minutes) and the t_{max} range is the same (0.75-3.0 h) between the test and reference product. Thus, no issue is raised. The clinical part of the study was conducted between 11 December 2017 and 20 December 2017 and the analytical part of the study was conducted between 19 January 2018 and 22 February 2018.

Results
The results from the statistical analysis for d-methylphenidate are presented in Table 1 below.

Table 1: Relative Bioavailability Results for D-methylphenidate (N = 63)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
$lnC_{max,0-3}$	2327.019	2549.782	91.3	87.05 - 95.68	16.0	100.0
$lnC_{max,3-24}$	3849.377	4458.055	86.3	82.75 - 90.10	14.4	100.0
$lnAUC_{0-3}$	4572.366	4948.363	92.4	88.83 - 96.11	13.3	100.0
$lnAUC_{3-24}$	35021.055	36036.551	97.2	93.54 - 100.97	12.9	100.0
$lnAUC_{0-t}$	39689.437	41133.238	96.5	93.06 - 100.05	12.2	100.0
$lnAUC_{0-\infty}$	41589.921	42309.272	98.3	94.77 - 101.97	12.3	100.0

For $Cmax_{,0-3}$, $Cmax_{,3-24}$, AUC_{0-3}, AUC_{3-24}, AUC_{0-t} and $AUC_{0-\infty}$ 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 d-methylphenidate.

Study 0715-16
Methods
This was a single-dose, two-way crossover study conducted in 68 healthy volunteers, comparing Methylphenidate, 54 mg, Prolonged-Release Tablets with CONCERTA®, 54 mg, Prolonged-Release Tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of l-methylphenidate and d-methylphenidate were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $Cmax_{,0-3}$, $Cmax_{,3-24}$, AUC_{0-3}, AUC_{3-24}, AUC_{0-t} and $AUC_{0-\infty}$ for d-methylphenidate. The statistical analysis was based on the more active d-enantiomer which is found acceptable. The clinical part of the study was conducted between 3 September 2017 and 02 October 2017 and the analytical part of the study was conducted between 04 October 2017 and 28 October 2017.

Results
The results from the statistical analysis for d-methylphenidate are presented in Table 2 below.

Table 2: Relative Bioavailability Results for D-methylphenidate (N = 63)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
$lnC_{max,0-3}$	8167.942	8652.764	94.4	89.73 - 99.31	17.2	100.0
$lnC_{max,3-24}$	14020.232	15752.516	89.0	85.85 - 92.27	12.2	100.0
$lnAUC_{0-3}$	15609.772	16542.212	94.4	90.48 - 98.41	14.2	100.0
$lnAUC_{3-24}$	134688.513	134273.768	100.3	97.44 - 103.26	9.8	100.0
$lnAUC_{0-t}$	150656.860	151366.526	99.5	96.89 - 102.24	9.0	100.0
$lnAUC_{0-\infty}$	159439.483	155909.630	102.3	99.57 - 105.03	9.0	100.0

For $Cmax_{,0-3}$, $Cmax_{,3-24}$, AUC_{0-3}, AUC_{3-24}, AUC_{0-t} and $AUC_{0-\infty}$ 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 d-methylphenidate.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**) a statistical evaluation of t_{max} is not required. However, if rapid release is claimed to be clinically relevant and importance for onset of action or is related to adverse events, there should be no apparent difference in median t_{max} and its variability between test and reference product. Methylphenidate is assessed as a medicinal product where rapid release is claimed to be clinically relevant and it was observed that the test product has a later t_{max} (3.000h) in comparison to the originator Concerta (1.667h) in the first phase. However, it could be agreed that t_{max} is not the most optimal parameter to detect a potential difference between the test and reference product in this case. In order to better describe a potential difference in the plasma concentration profile in the first phase between the test and reference product, ratio and 90% confidence interval at 1 hour, 2 hours and 3hours as well as $AUC_{0-1.667h}$ (i.e. AUC up to median tmax of reference product) was presented, see table below.

	C1h	C2h	C3h	AUC0-1.667
Ratio (%)	89.2	94.2	108.1	88.8
Lower 90% CI	79.88	90.66	103.00	81.39
Upper 90% CI	99.60	97.88	113.41	96.87

From these data it could be concluded that the test and reference product are sufficiently similar in the first phase.

Study 0714-16

Methods

This was a single-dose, two-way crossover study conducted in 67 healthy volunteers, comparing Methylphenidate, 54 mg, Prolonged-Release Tablets with Concerta® 54 mg, Prolonged-Release Tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of l-methylphenidate and d-methylphenidate were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $Cmax_{,0-4}$, $Cmax_{,4-24}$, AUC_{0-4}, AUC_{4-24}, AUC_{0-t} and $AUC_{0-\infty}$. The statistical analysis was based on the more active d-enantiomer which is found acceptable. The absorption of methylphenidate following administration of the test product is a little bit slower than the reference product in the first phase for d-methylphenidate based on the median t_{max} values (test: 4.0h and ref: 3.667h). However, the difference in t_{max} is assessed as small (20 minutes) and the t_{max} range is the same (0.667-4.0h) between the test and reference product. Thus, no issue is raised. The clinical part of the study was conducted between 7 June 2017 and 26 June 2017 and the analytical part of the study was conducted between 27 July 2017 and 15 August 2017.

Results

The results from the statistical analysis are presented in Table 3 below.

Table 3: Relative Bioavailability Results for D-methylphenidate (N = 61)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
$lnC_{max,0-4}$	11748.707	11692.480	100.5	94.00 - 107.41	22.2	100.0
$lnC_{max,4-24}$	15740.703	17176.209	91.6	88.77 - 94.61	10.5	100.0
$lnAUC_{0-4}$	25872.031	27660.950	93.5	86.37 - 101.29	26.7	99.8
$lnAUC_{4-24}$	156651.970	157149.274	99.7	97.58 - 101.83	7.0	100.0
$lnAUC_{0-t}$	183958.028	186394.686	98.7	96.89 - 100.52	6.1	100.0
$lnAUC_{0-\infty}$	192128.290	191294.268	100.4	98.60 - 102.31	6.1	100.0

For $Cmax_{,0-4}$, $Cmax_{,4-24}$, AUC_{0-4}, AUC_{4-24}, AUC_{0-t} and $AUC_{0-\infty}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% or d-methylphenidate.

Discussion and overall conclusion

A single dose bioequivalence study during fed condition on the highest 54 mg strength is found sufficient, since no food effect is expected for this type of formulation.

No multiple dose study was performed by the applicant and no multiple dose study is considered necessary since low accumulation was demonstrated in the two single dose studies performed at the highest 54 mg strength under both fasting and fed condition.

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence studies, Methylphenidate, Prolonged-Release Tablets is considered bioequivalent with Concerta, Prolonged-Release Tablets.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Methylphenidate Xiromed.

Safety specification

The MAH has submitted the version 1.0 RMP dated 28 Oct 2020 and proposed the following safety concerns:

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

Pharmacovigilance Plan

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

Risk minimisation measures
Collapsed version:

Important identified risk:
Serious cardiovascular events
Psychosis/mania
Verbal or motoric tics
Depression
Aggression
Drug abuse/Drug dependence
Withdrawal syndrome
Decreased rate of growth
Seizures
Cerebrovascular disorders

Routine risk minimisation measures:
Information in SmPC and PL.

Additional Risk Minimisation Measures:
The educational material for Methylphenidate Xiromed 18 mg & 54 mg depot tabletter is available for healthcare professionals at http://www.methylphenidate-guide.eu/landing/ and the MAH is expected to join the collaboration to manage the website.

Educational material for healthcare professionals
There are additional risk minimisation activities to educate healthcare professionals on the safe use of methylphenidate by providing educational material for the safety concerns listed above.
Key elements:

- **Physician's guide to prescribing**

  Key messages and information: Intoduction to ADHD and comprehensive treatment programme.

- **Checklist 1: methylphenidate checklist before prescribing**

  Key messages and information:

  - Blood pressure and pulse should be recorded at each adjustment of dose and then at least every 6 months
  - Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart
  - Development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit

  Checklist for contraindications and special warnings and precautions for use.

- **Checklist 2: methylphenidate checklist for monitoring of ongoing therapy**

  Key messages and information:

  - Blood pressure and pulse should be recorded at each adjustment of dose and then at least every 6 months
  - Height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart
  - Development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit

  Checklist for monitoring of general medical findings, new cardiovascular findings, new neurological findings, new psychiatric findings or worsening there of, treatment duration, end of treatment.

- **Chart for ongoing monitoring during methylphenidate treatment**

  Key messages and information:

  - Blood pressure and pulse should be recorded at each adjustment of dose and then at least every 6 months
  - Height, weight and appetite should be recorded at least 6-monthly with maintenance of a growth chart
  - Development of de novo or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit

  Chart for monitoring blood pressure, heart rate, body weight and height, and appetite.

Summary of the RMP

The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The Summary of safety concerns and the risk minimisation measures have been updated in line with the reference product.

Target audience and planned distribution path:
The details of the communication plan will be agreed with each national competent authority prior to the launch of the product. The main target audience of the educational material include specialists involved with diagnosis and initiation of methylphenidate treatment, and physicians involved with follow-up of the treatment. The distribution path will include mailing of the printed material and/or electronic access to the material.

The applicant has agreed to join the collaboration to manage the website http://www.methylphenidate-guide.eu/landing/ where the educational material is made available for healthcare professionals.

The submitted Risk Management Plan, version 1.0 signed 28 Oct 2020 is considered acceptable. The RMP is in line with the latest version 8.1 for Concerta.

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 MPA;
- 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 Spanish.
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, Methylphenidate Xiromed, is found adequate. There are no objections to approval of Methylphenidate Xiromed, 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 application is therefore recommended for approval.

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

N/A

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

- **Additional risk minimisation measures (including educational material)**
  The educational material should contain the following key elements:

  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

  As part of the EU Article 31 referral conditions, MAHs of methylphenidate-containing products for ADHD were requested to produce a fully harmonised risk minimisation tool (ie, the Educational Tool that includes a physician's guide to prescribing and prescriber's checklists) containing all of the important information from the Clinical Particulars section of the EU core SmPC. The physician's guide to prescribing and prescriber's checklists should be made available to healthcare providers via a website where they may be downloaded.

VII. APPROVAL

Methylphenidate Xiromed, 18 mg and 54 mg, prolonged-release tablet was approved in the national procedure on 20210126.

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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
5.4.3-2022-102294	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	2023.03.30	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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se