LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Methylphenidate Orion
# (methylphenidate hydrochloride)

## SE/H/1917/01/DC
## SE/H/1917/04/DC

## Asp. No: 2018-1274, 2018-1271

**This module reflects the scientific discussion for the approval of Methylphenidate Orion. The procedure was finalised on 2020-04-20. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

The application for Methylphenidate Orion, 18 mg and 54 mg, prolonged-release tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI 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 and 54 mg, prolonged-release tablets, authorised in SE since 2002, with Janssen-Cilag AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Concerta XL, 18 mg and 54 mg, prolonged-release tablets from UK with Janssen-Cilag Ltd as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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 physio-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 18mg strength under fasting condition and two bioequivalence studies were performed at the 54mg 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.

BE Study for 18 mg under fasting conditions
*Methods*
This was a single-dose, two-way crossover study conducted in 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 during 2017 and the analytical part of the study was conducted during 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

| 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.

BE Study for 54 mg under fasting conditions
*Methods*
This was a single-dose, two-way crossover study conducted in 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 and the analytical part of the study was conducted during 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

| 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 3 hours as well as $AUC_{0\text{-}1.667h\ (i.e.\ AUC\ up\ to\ median\ tmax\ of\ reference\ product)}$ 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.

BE Study for 54 mg under fed conditions

*Methods*

This was a single-dose, two-way crossover study conducted in 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 and the analytical part of the study was conducted during 2017.

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

Table 3: Relative Bioavailability Results for D-methylphenidate

| 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.

In summary, the lowest 18mg strength and the highest 54mg strength is found approvable.

## 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 Orion.

Safety specification
The MAH has submitted a Risk Management Plan, version 1.2 signed 1 April 2020, with the following proposed summary of safety concerns:

| Summary of safety concerns | |
|---|---|
| Important identified risks | • Serious cardiovascular events<br>• Psychosis/mania<br>• Verbal or motoric tics<br>• Depression |

| Summary of safety concerns | |
|---|---|
| | • Aggression<br>• Drug abuse/Drug dependence<br>• Withdrawal syndrome<br>• Reduced weight gain<br>• Decreased rate of growth<br>• Seizures<br>• Cerebrovascular disorders |
| Important potential risks | • Suicidality<br>• 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

Summary of risk minimisation measures is in line with the latest RMP (v8.1) for the reference product Concerta and is presented in the table below:

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Important identified risk:<br><br>Serious cardiovascular events | Routine risk minimisation measures:<br><br>Information in SmPC sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 4.9, and PL sections 2, 3 and 4.<br><br>Additional risk minimisation measures:<br><br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None |
| Important identified risk:<br><br>Psychosis/mania | Routine risk minimisation measures:<br><br>Information in SmPC sections 4.2, 4.3, 4.4 and 4.8, and PL section 2, 3 and 4.<br><br>Additional risk minimisation measures:<br><br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None |
| Important identified risk:<br><br>Verbal or motoric tics | Routine risk minimisation measures:<br><br>Information in SmPC sections 4.2, 4.4 and 4.8, and PL sections 2, 3 and 4. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | Additional risk minimisation measures:<br>Educational material for healthcare professionals | |
| Important identified risk:<br>Depression | Routine risk minimisation measures:<br>Information in SmPC sections 4.2, 4.3, 4.4 and 4.8, and PL sections 2, 3 and 4.<br>Additional risk minimisation measures:<br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |
| Important identified risk:<br>Aggression | Routine risk minimisation measures:<br>Information in SmPC sections 4.2, 4.4 and 4.8, and PL sections 2, 3 and 4.<br>Additional risk minimisation measures:<br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |
| Important identified risk:<br>Drug abuse/Drug dependence | Routine risk minimisation measures:<br>Information in SmPC sections 4.2, 4.4 and 4.8, and PL sections 2 and 3.<br>Additional risk minimisation measures:<br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |
| Important identified risk:<br>Withdrawal syndrome | Routine risk minimisation measures:<br>Information in SmPC section 4.4 , and PL section 3.<br>Additional risk minimisation measures:<br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None |
| Important identified risk:<br>Reduced weight gain | Routine risk minimisation measures:<br>Information in SmPC sections 4.2, 4.4 and 4.8, and PL sections 3 and 4. | Routine pharmacovigilance activities beyond adverse |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | Additional risk minimisation measures:<br><br>Educational material for healthcare professionals | reactions reporting and signal detection:<br><br>None |
| Important identified risk:<br><br>Decreased rate of growth | Routine risk minimisation measures:<br><br>Information in SmPC sections 4.2, 4.4 and 4.8, and PL sections 3 and 4.<br><br>Additional risk minimisation measures:<br><br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None |
| Important identified risk:<br><br>Seizures | Routine risk minimisation measures:<br><br>Information in SmPC sections 4.4 and 4.8, and PL sections 2 and 4.<br><br>Additional risk minimisation measures:<br><br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None |
| Important identified risk:<br><br>Cerebrovascular disorders | Routine risk minimisation measures:<br><br>Information in SmPC sections 4.3, 4.4, 4.5 and 4.8, and PL sections 2, 3 and 4.<br><br>Additional risk minimisation measures:<br><br>Educational material for healthcare professionals | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None |

Summary of the RMP

The submitted Risk Management Plan, version 1.2 signed 1 April 2020, is considered to be acceptable.

# V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Concerta XL 27 mg prolonged release tablets, DE/H/6007/004. They also performed a bridging report concerning design/layout making reference to Burana gel (Orion house style lay-out), DE/H/5281/01/DC. The bridging reports submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Methylphenidate Orion is approvable from a non-clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated for the 18 mg and 54 mg strengths.

The benefit/risk ratio is considered positive and Methylphenidate Orion, 18 mg and 54 mg, prolonged-release tablets is 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

# VII. APPROVAL

The decentralised procedure for Methylphenidate Orion, 18 mg and 54 mg, prolonged-release tablets was positively finalised on 2020-04-20.

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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/1917/IB/08/G | Type IAIN C.I.3.a: To implement the outcome of PSUSA procedure (PSUSA/00002024/202110).<br><br>Type IB C.I.11.z RMP update:<br>In connection of PSUSA (PSUSA/00002024/202110) PRAC recommended to remove additional risk minimisation measures (aRMMs) from the Risk Management Plan (RMP). According to PRAC recommendation, following educational materials for healthcare professionals (aRMMs) have been removed from the RMP:<br>- Physician's guide to prescribing<br>- Checklist 1: methylphenidate checklist before prescribing<br>- Checklist 2: methylphenidate checklist for monitoring of ongoing therapy<br>- Chart for ongoing monitoring during methylphenidate treatment<br><br>Above mentioned aRMMs have been conditions (pursuant to Article 21a of Directive 2001/83/EC) to the marketing authorisations of Methlyphenidate Orion. According to CMDh Q&A on Pharmacovigilance, changes to conditions don't need an own variation, but can be done within respective variation concerning updates to RMP. Therefore, the conditions to marketing authorisations are deleted in this variation. There are no other conditions to MAs of Methylphenidate Orion.<br><br>In addition, RMP has been amended based on the reference product, Concerta. | Yes | 2023-02-24 | Approval | **Variation type IAIN no C.I.3.a:**<br>The Applicant has updated the product information according to the outcome of PSUSA/00002024/202110.<br><br>**Variation type IB no C.I.11.z:**<br>The Applicant has submitted an updated Risk Management Plan for Methylphenidate Orion. Following updates have been proposed:<br>- Update of safety concerns according to the latest reference product (Concerta) RMP summary.<br>- Removal of additional risk minimization measures based on CMDh recommendation on PRAC recommendations on PSUSA/00002024/202110.<br>The submitted RMP, version 3.1 dated 04 January 2023, is considered acceptable.<br><br>The following conditions to the Marketing Authorisation have been lifted as a result of this variation application:<br><br>**Additional risk minimisation measures - Educational material**<br>**Physician educational tool:**<br>*Methylphenidate physician's guide to prescribing consisting of:*<br>• Introductory letter<br>• Checklist 1: Methylphenidate checklist before prescribing<br>• Checklist 2: Methylphenidate checklist for monitoring of ongoing therapy<br>• Chart for ongoing monitoring during methylphenidate treatment |

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