LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Phenichem
(methylphenidate hydrochloride)

SE/H/1912/01-04/DC

This module reflects the scientific discussion for the approval of Phenichem. The procedure was finalised on 2021-11-29. 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 Phenichem, 18 mg, 27 mg, 36 mg, 54 mg, prolonged-release tablet.

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 Phenichem, 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Laboratorios Liconsa S.A., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and ES, PL and UK(NI) as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Concerta, 18 mg, 27 mg, 36 mg and 54 mg, prolonged-release tablets, authorised in SE since 2002, 2008, 2002 and 2002 respectively, with Janssen-Cilag AB as marketing authorisation holder.

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

European Reference Product (ERP)
A European Reference Product is used in CMS PL (SE/H/1912/02/DC and SE/H/1912/04/DC): Concerta, 27 mg, prolonged-release tablet, authorised in SE since 2008, with Janssen-Cilag AB as marketing authorisation holder; and Concerta, 54 mg, prolonged-release tablet, authorised in SE since 2002, with Janssen-Cilag AB as marketing authorisation holder, respectively.
The ERP information was provided by the RMS during the 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 hydrochloride are well known. As methylphenidate hydrochloride 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 Phenichem 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 Phenichem from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted six single dose bioequivalence 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)**

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. Pharmacokinetic parameters 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. It is also observed that the absorption of methylphenidate following administration of the test product is slower than the reference product in the first phase based on the median t_{max} value for d-methylphenidate. 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. Pharmacokinetic parameters 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 of 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 $AUC_{0-1.667h}$ (i.e. AUC up to median t_{max} of reference product) was presented in Table 3.

Table 3. Ratio and 90% CI Test vs RLD for plasmatic concentrations at 1, 2, 3 h and partial AUC up to median Tmax of Ref.

	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

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. It is currently unclear if the meal is a high-fat and high-calorie meal, see list of questions. 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 4 below.

Table 4. Pharmacokinetic parameters 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.

Study 0104-20
Methods
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 80 healthy volunteers under fasting conditions. After an overnight fast one tablet of 27 mg of either test or reference was administered together with 240 ml of water. 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 $AUC_{0-\infty}$. The statistical analysis was based on the more active d-enantiomer which is found acceptable. The clinical part of the study was conducted between 08 January 2021and 22 January 2021 and the analytical part of the study was conducted between 10 February 2021 and 02 March 2021.

Results
The results from the statistical analysis are presented in Table 5 below.

Table 5. Pharmacokinetic parameters for d-Methylphenidate, n=74

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%		
$lnC_{max,0-3}$	4050.397	3999.785	101.3	98.11 - 104.52	11.6
$lnC_{max,3-t}$	6764.332	7228.510	93.6	90.49 - 96.77	12.3
$lnAUC_{0-3}$	7329.218	7865.931	93.2	88.49 - 98.12	19.0
$lnAUC_{3-t}$	73462.103	79481.191	92.4	88.70 - 96.31	15.1
$lnAUC_{0-t}$	81250.889	87696.434	92.7	89.33 - 96.09	13.4
$lnAUC_{0-\infty}$	87315.848	92898.569	94.0	90.39 - 97.73	14.3

Bioequivalence was demonstrated for $C_{max,0-3}$, $C_{max,3-24}$, 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 all the above parameters.

Study 0105-20

Methods

The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 80 healthy volunteers under fasting conditions. After an overnight fast one tablet of 36 mg of either test or reference was administered together with 240 ml of water. 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, AUC0-3, AUC3-24, AUC0-t and AUC0-∞. The statistical analysis was based on the more active d-enantiomer which is found acceptable. The clinical part of the study was conducted between 16 January 2021 and 29 January 2021 and the analytical part of the study was conducted between 23 February 2021 and 19 March 2021.

Results

The results from the statistical analysis are presented in
Table 6 below.

Table 6. Pharmacokinetic parameters for d-Methylphenidate, n=76.

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
$lnC_{max,0-3}$	5463.229	5161.937	105.8	102.25 - 109.55	12.8	100.0
$lnC_{max,3-t}$	8636.379	9416.088	91.7	89.01 - 94.51	11.1	100.0
$lnAUC_{0-3}$	10038.737	9692.546	103.6	99.47 - 107.84	15.0	100.0
$lnAUC_{3-t}$	99864.288	103901.602	96.1	93.23 - 99.09	11.3	100.0
$lnAUC_{0-t}$	110242.588	113965.130	96.7	94.06 - 99.48	10.4	100.0
$lnAUC_{0-\infty}$^	118896.524	120128.441	99.0	95.88 - 102.17	11.7	100.0

Bioequivalence was demonstrated for $C_{max,0-3}$, $C_{max,3-24}$, 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 all the above parameters.

Study 0106-20

Methods

The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 80 healthy volunteers under fed conditions. After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed completely within 30 minutes. A single oral dose (18 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. 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, AUC0-4, AUC4-24, AUC0-t and AUC0-∞. The statistical analysis was based on the more active d-enantiomer which is found acceptable. The clinical part of the study was conducted between 22 January 2021 and 04 February 2021 and the analytical part of the study was conducted between 11 February 2021 and 23 March 2021.

Results

The results from the statistical analysis are presented in Table 7 below.

Table 7. Pharmacokinetic parameters for d-Methylphenidate, n=77

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %		
$lnC_{max,0-4}$	3277.726	3028.791	108.2	102.30 - 114.48	21.2
$lnC_{max,4-t}$	4659.318	4895.179	95.2	91.90 - 98.58	13.1
$lnAUC_{0-4}$	6200.642	5650.255	109.7	100.86 - 119.40	32.2
$lnAUC_{4-t}$	47438.712	49618.307	95.6	92.86 - 98.43	10.9
$lnAUC_{0-t}$	54137.150	56070.439	96.6	94.17 - 99.00	9.3
$lnAUC_{0-\infty}$	57860.682	58885.764	98.3	95.82 - 100.76	9.4

Bioequivalence was demonstrated for $C_{max,0-4}$, $C_{max,4-24}$, 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% for all the above parameters.

Discussion and overall conclusion

To support the application, the applicant has submitted six single dose bioequivalence studies. Based on these bioequivalence studies, Phenichem, 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.

Methylphenidate is assessed to be medicinal product where rapid release is claimed to be clinically relevant. In Study 0715-16, 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. To demonstrate similar absorption phase between test and reference, the company presented the ratio and 90% confidence interval at 1 hour, 2 hours and 3 hours as well as AUC0-1.667h (i.e. AUC up to median t_{max} of reference product). From these data it could be concluded that the test and reference product are sufficiently similar in the first phase and the issue is considered as resolved.

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. This is agreed.

From a pharmacokinetic point of view, the provided information is acceptble.

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 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 Phenichem.

The MAH has submitted the risk management plan (RMP) version 0,3 signed 9 September 2021 and proposed the following summary safety concerns:

Table SVIII.1: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

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 0,3 signed 9 September 2021 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
Routine risk minimisation is suggested and additional risk minimisation measures (educational material) are proposed by the applicant, which is endorsed.

Physician educational tool:

Methylphenidate physician's guide to prescribing and prescriber's checklists 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

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 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, Phenichem, is found adequate. There are no objections to approval of the above-mentioned products, from a non-clinical and clinical point of view. Bioequivalence between the test and reference products has been adequately demonstrated. The product information is acceptable. The application is therefore 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 (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

The decentralised procedure for Phenichem, 18 mg, 27 mg, 36 mg, 54 mg, prolonged-release tablet was positively finalised on 2022-11-29.

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/1912/01-04/IB/06	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

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