LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Methylphenidate Alternova

(methylphenidate hydrochloride)

Asp no: 2014-1206, 2014-1207, 2014-1208

This module reflects the scientific discussion for the approval of Methylphenidate Alternova. Please note that the marketing authorisation was first approved with the name "Methylphenidate E Consult" and therefore this name is used throughout the document. The procedure was finalised on 2015-07-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Methylphenidate E Consult, 10mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The application for Methylphenidate E Consult, 5mg, 20mg, tablet is a hybrid application made according to Article 10(3) of Directive 2001/83/EC.

The applicant E Consult ApS applies for a marketing authorisation in Sweden through a National procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ritalin 10 mg tablets authorised in DK since 1956, with Novartis Healthcare A/S as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

Methylphenidate is given as a racemate consisting of d-threo methylphenidate and l-threo methylphenidate. D-methylphenidate has an oral bioavailability of 22 ± 8% while l-methylphenidate has an oral bioavailability of 5±3 %. The d-enantiomer is considered to be the pharmacologically active enantiomer. Following an oral dose of methylphenidate maximal plasma concentrations occur at approximately 1-2 hours in adults.

The pharmacokinetics of methylphenidate is not affected by food in a clinically relevant way, and therefore there are no restrictions with respect to food in the SmPC of the originator.

The pharmacokinetics of methylphenidate is linear up to a dose of 20 mg.

The terminal half-life in adults is approximately 3 hours. Mean clearance following an IV dose of methylphenidate is 0.40 l/h/kg for d-methylphenidate and 0.73 l/kg/h for l-methylphenidate.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Methylphenidate, 10 mg, tablets with Ritalin, 10 mg, tablets under fasting conditions. Both products were given at a dose of 20 mg (2x10 mg). Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable.

Plasma concentrations of methylphenidate were determined with an adequately validated LC/MS/MS method. An achiral analytical method was used. It is known that the enantiomers have different pharmacokinetic properties (different clearance and different absolute bioavailability due to different first pass effect), but the absorption is fast with similar t_{max} values for both enantiomers indicating no obvious difference in absorption between enantiomers. The d-enantiomer is considered to be the pharmacologically active enantiomer and thus it would be sufficient to demonstrate bioequivalence for this enantiomer. Since the l-enantiomer is more rapidly eliminated, the active d-form will dominate in plasma. In addition, the results from the current study show very similar t_{max}-values between test and reference and the confidence intervals for AUC and C_{max} are very narrow with ratios close to one. Thus, it is not considered likely that a chiral method would result in a different conclusion regarding bioequivalence and the use of an achiral method is found acceptable.

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for methylphenidate, n=35.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**58849±19214**	**12865±3155**	**1.50 (0.75-2.50)**
Reference	**58123±17228**	**12940±3235**	**1.50 (0.50-2.00)**
***Ratio (90% CI)**	**100.25 (97.33-103.25)**	**99.76 (94.60-105.21)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Based on the submitted bioequivalence study, Methylphenidate E Consult 10 mg tablets are considered bioequivalent with Ritalin 10 mg tablets.

From a pharmacokinetic point of view, absence of studies with the additional strengths 5 mg and 20 mg is acceptable, as the pharmacokinetics of methylphenidate is linear up to a dose of 20 mg and since the active substance is highly soluble. In addition, the given dose of 20 mg (2x10 mg) corresponds to the highest strength. Absence of studies with the additional strengths is also acceptable from a quality perspective.

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 E Consult.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	Hypertension Tachycardia Raynaud's phenomenon Psychosis/mania Hallucinations Anorexia Decreased rate of growth Aggression

	Depression
Important potential risks	QT prolongation Arrhythmias Ischemic cardiac events Cyanosis Sudden death Cerebrovascular disorders Hostility Suicidality Repetitive behaviours Migraine Tics/Tourette's syndrome/dystonias Effect on final height Sexual maturation (delayed) Drug abuse and drug dependence Withdrawal syndrome Diversion Off-label use Carcinogenicity Lymphocytic leukemia Neonatal cardio-respiratory toxicity Effect on neonatal growth Cardiomyopathy
Missing information	None

Risk minimisation measures

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP

Safety concern	***Routine risk minimisation measures***	***Additional risk minimisation measures***
Important identified risks		
Hypertension	SmPC: Posology (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Tachycardia	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Raynaud's phenomenon	SmPC: Undesirable effects (Sec 4.8)	Routine risk minimisation is considered sufficient at this time
Psychosis/mania	SmPC: Posology (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Hallucinations	SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.

Anorexia	SmPC: Posology (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Decreased rate of growth	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Aggression	SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Depression	SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Important potential risks		
QT prolongation	This potential risk is not listed in the SmPC	Routine risk minimisation is considered sufficient at this time
Arrhythmias	SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Ischemic cardiac events	SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Cyanosis	This potential risk is not listed in the SmPC	Routine risk minimisation is considered sufficient at this time
Sudden death	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Cerebrovascular disorders	SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Hostility	SmPC: Special warnings and precautions for use (Sec 4.4)	Physician's educational material directed to the prescriber or through a MPH website.
Suicidality	SmPC: Contraindications (Sec 4.3) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Repetitive behaviors	SmPC: Undesirable effects (Sec 4.8)	Routine risk minimisation is considered sufficient at this time
Migraine	SmPC: Undesirable effects (Sec 4.8)	Routine risk minimisation is considered sufficient at this time
Tics/Tourette's syndrome/dystonias	SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Effect on final height	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4)	Routine risk minimisation is considered sufficient at this time
Sexual maturation (delayed)	This potential risk is not listed in the SmPC	Routine risk minimisation is considered sufficient at this time

Drug abuse and drug dependence	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	Physician's educational material directed to the prescriber or through a MPH website.
Withdrawal syndrome	SmPC: Special warnings and precautions for use (Sec 4.4)	Physician's educational material directed to the prescriber or through a MPH website.
Diversion	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4)	Physician's educational material directed to the prescriber or through a MPH website.
Off-label use	SmPC: Posology (Sec 4.2) SmPC: Special warnings and precautions for use (Sec 4.4)	Physician's educational material directed to the prescriber or through a MPH website.
Carcinogenicity	SmPC: Preclinical safety data (Sec 5.3)	Routine risk minimisation is considered sufficient at this time
Lymphocytic leukemia	This potential risk is not listed in the SmPC	Routine risk minimisation is considered sufficient at this time
Neonatal cardio-respiratory toxicity	SmPC: Pregnancy and lactation (Sec 4.6)	Routine risk minimisation is considered sufficient at this time
Effects on neonatal growth	SmPC: Pregnancy and lactation (Sec 4.6)	Routine risk minimisation is considered sufficient at this time
Cardiomyopathy	This potential risk is not listed in the SmPC	Routine risk minimisation is considered sufficient at this time
Missing information		
None	N/A	N/A

Summary of the RMP

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly. The RMP is approved.

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 (PIL) has been performed on the basis of a bridging report making reference to (for text content) Ritalin tablets (Ritalin and other methylphenidate containing medicinal products were user tested after the finalisation of the Article 31 Referral in October 2009) and (for lay-out)

Hydroxocobalamin E Consult, user tested in national procedure 5.4.1-2013-64373. 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 Methylphenidate E Consult, 5mg, 10mg, 20mg, tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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:
  - Physicians guide to prescribing
  - Checklists for actions before prescribing and for monitoring of ongoing therapy

VII. APPROVAL

Methylphenidate E Consult, 5mg, 10mg, 20mg, tablet was approved in the national procedure on 2015-07-16.

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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
5.4.3-2022-105879	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	2023.03.31	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)