Mutual Recognition Procedure

Public Assessment Report

Medikinet 5 / 10 / 20 mg Tabletten
Medikinet retard 10 / 20 / 30 / 40 mg

Methylphenidate hydrochloride

DE/H/0690/001-007/MR

This module reflects the scientific discussion for the approval of Medikinet tablets and Medikinet retard prolonged release capsule. The procedure was finalised at 11th September 2006. For information on changes after this date please refer to the module 'Update'.

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Medikinet 5 / 10 / 20 mg Tabletten Medikinet retard 10 / 20 / 30 / 40 mg
Name of the drug substance (INN name):	Methylphenidate
Pharmaco-therapeutic group (ATC Code):	N06BA04
Pharmaceutical form(s) and strength(s):	Tablet; 5 / 10 / 20 mg Capsule; 10 / 20 / 30 / 40 mg
Reference Number(s) for the Decentralised Procedure	DE/H/0690/001-007/MR
Reference Member State:	DE
Concerned Member States:	DE/H/0690/001-003: DK, ES, FI, LU, NL, NO, PL, SE, UK DE/H/0690/004-007: AT, DK, ES, FI, LU, NL, NO, PL, SE, UK

I. INTRODUCTION

This hybrid application for marketing authorisation concerns Medikinet tablets and Medikinet prolonged release capsules.
The tablets are claimed to be essentially similar to Ritalin® 10 mg tablets (Novartis Pharma GmbH, Germany).
For the prolonged release capsules a full application was filed containing comprehensive pharmacokinetic, efficacy and safety studies.

The products are indicated for the treatment and management of hyperkinetic disorder or attention deficit hyperactivity disorder (ADHD) in children from the age of six and in adolescents as part of a comprehensive treatment programme if other therapeutic measures alone have proved inadequate.

The indication was changed by a variation approved on 17th November 2017:
Attention-Deficit/Hyperactivity Disorder (ADHD)

Medikinet retard is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over and adults when remedial measures alone prove insufficient.

Treatment must should be initiated and supervised by a doctor specialised specializing in the treatment of ADHD such as an expert paediatricianpediatrics, a child and adolescent psychiatrists or a psychiatrists. Treatment must be initiated under the supervision of a specialist in childhood behaviour disorders.

II. QUALITY ASPECTS

II.1 Introduction

Medikinet is presented in the form of immediate-release (IR) tablets containing 5, 10, 20 mg methylphenidate hydrochloride.
The excipients are Microcrystalline cellulose, Pregelatinised maize starch, Calcium hydrogen phosphate dihydrate, Lactose monohydrate, Magnesium stearate

The four strengths of Medikinet retard capsules (10, 20, 30 and 40 mg, modified release [MR]) reflect the available strengths and posology of IR methylphenidate formulations (5, 10, and 20 mg, maximum daily dose 60 mg) in order to facilitate transferring children from the IR to the milligram equivalent of the MR formulations.
The excipients of the capsule filling are sugar spheres consisting of (sucrose and maize starch), poly(vinyl alcohol), macrogol, polysorbate, talc, eudragit L, sodium hydroxide, triethyl citrate, indigo carmine, simeticone emulsion, methylcellulose, sorbic acid, silica, colloidal anhydrous.
The hard gelatine capsules are made of gelatine, sodium laurylsulphate and purified water and are coloured respectively to the different strenghts with titanium dioxide (E 171), erythrosin (E 127) patent blue V (E 131), black iron oxide (E 172), indigo carmine (E 132).

The tablets and capsules are packed in PVC blister packs with PVdC-coating heat sealed with aluminium push through foil.

II.2 Drug substance

As there is no monograph available in the European Pharmacopoeia (Ph. Eur.) for methylphenidate hydrochloride, the manufacturers refer to the current monograph of the USP. The manufacturer of the finished product established a comprehensive overall specification for the drug substance.
Methylphenidathydrochloride is a white, odourless, fine, crystalline powder.

II.3 Drug product

Tablets

The immediate release tablets base on straight forward preparation manufactured in standard process.

Capsules

The preparation consists of immediate release and enteric coated pellets. In each capsule 50% of these pellets are uncoated, so as to trigger the immediate release of the active component. The other 50% are enteric coated to ensure gastric acid resistance, which will lead to the sustained release of methylphenidate hydrochloride. This technique combines rapid onset of action with a long-acting effect

All excipients used in the medical products meet the requirements of the Ph. Eur. monographs, except for simeticone emulsion which is controlled by the requirements of the USP. The manufacturing process has been sufficiently described and critical steps are identified. Results from process validation studies confirm that the process is under control and ensure the quality of the finished product in relation to its intended purpose.
Batch analysis results show that the finished products meet the specifications proposed.

Stability studies under ICH conditions have been performed. The proposed shelf-life of 30 months for the storage condition "*Do not store above 25 °C" (tablets)* and respectively "*Do not store above 30 °C" (capsules)* is accepted.

The Reference Member State has been assured that acceptable standards of GMP are in place for these product types at the site responsible for the manufacture and assembly of this product prior to granting its national authorisation.

III. NON-CLINICAL ASPECTS

Reference is made to the Summary of Product Characteristics (sections 5.1, 5.2, 5.3 as well as 4.6) where the current knowledge of Methylphenidate hydrochloride is well described.

Tablets

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.

Capsules

No new toxicological aspect raises from the modified release formulation in comparison with the immediate release tablet if it is taken as prescribed with a meal.

IV. CLINICAL ASPECTS

IV.1 Introduction

Methylphenidate hydrochloride (MPH) is an indirect-acting sympathomimetic agent with stimulant effects on the central nervous system. It is used in the treatment and management of hyperactive children with attention-deficit hyperactivity disorder (ADHD), when remedial measures alone prove inadequate. It is marketed worldwide as well as in many countries of the EU for the treatment of attention deficit disorders and narcolepsy.

The German originator product, on which nearly all literature for ADHD is based, is Ritalin® (Immediate release tablets, Novartis Pharma). In Germany, Ritalin® has passed the re-registration procedure in 1997 and is therefore to be considered the adequate reference drug for bioavailability studies.

The four strengths of Medikinet retard capsules (10, 20, 30 and 40 mg) reflect the available strengths and posology of IR methylphenidate formulations (5, 10, and 20 mg, maximum daily dose 60 mg) in order to facilitate transferring children from the IR to the milligram equivalent of the MR

formulations. Since the capsule filling is divided in an immediate release and sustained release part a biphasic plasma level profile is anticipated.

Der Hinweis erscheint mir nicht wirklich erforderlich, da er nichts mit Medikinet oder der Zulassungsentscheidung zu tun hat im Sinne einer Bezugnahme. Eher wäre hier eine Anmerkung zu Equasym notwendig, um die Relevanz der BV-Studien zu erklären.

IV.2 Pharmacodynamics and Pharmacokinetics

Reference is made to the Summary of Product Characteristics (sections 5.1 and 5.2) where the pharmacodynamic and pharmacokinetic properties of Methylphenidate are well described.

IV.3 Clinical efficacy and safety

Tablets

Clinical efficacy and safety

Since this product has been shown to be essentially similar and refers 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.

Bioequivalence

Three studies have been performed to demonstrate the bioequivalence of Medikinet tablets with the reference products Ritalin and one study versus Equasym.

Study results of all these bioequivalence studies showed that the criteria used to estimate bioequivalence between Methylphenidate hydrochloride 5 mg, 10 mg and 20 mg Tablets and Ritalin® (Novartis Pharma, Germany) are all fulfilled. In fact, the 90% confidence intervals of the relative means of AUC_t, AUC_∞ and C_{max} and of $AUC_{0-\infty}$, C_{max}, and t_{max} of the Test to the Reference formulation were within the acceptance range in of 80 - 125% as required by the CPMP guideline. Study results of the fourth bioequivalence study also showed that the criteria used to estimate bioequivalence between Methylphenidathydrochlorid 5 mg Tabletten and Equasym® (Celltech Pharma, Germany) were fulfilled.

Based on these results, it can been concluded that a single dose of methylphenidate hydrochloride tablets of the applicant (Medice Arzneimittel) is bioequivalent to a single dose of Ritalin® (Novartis Pharma GmbH, Germany) and of Equasym® (Celltech Pharm, Germany) under fasting conditions.

As a conclusion, Methylphenidate hydrochloride 5 mg, 10 mg and 20 mg Tablets can be judged to have the same bioavailability as Ritalin® and Methylphenidate hydrochloride 5 mg can be judged to have the same bioavailability as Equasym® 5 mg.
The same therapeutic indications, contra-indications, warnings and precautions for use should be applied for Methylphenidate hydrochloride 5 mg, 10 mg and 20 mg Tablets as for Ritalin® and Equasym®.

Prolonged Release Capsules

Clinical efficacy

The efficacy of Medikinet retard and its suitability for single-dosing in the morning to solve compliance problems in school children can be assumed. Superiority over placebo and non-inferiority to immediate releases products has been proven in two controlled clinical trials following current methodological standards.
The prolonged release capsule might be slightly less efficacious than immediate release methylphenidate at certain time points during the day although no clinically important differences were seen. Methylphenidate has shown to diminish behaviours prototypical of ADHD. It reduces motor activity, enhances attention, and improves social behaviour. Also associated behaviours including on-task-behaviour, academic performance, and social function have been shown to be improved by treatment with methylphenidate. These effects appear to be dose-dependent and cross-sectional including home, clinic and school.
As bioequivalence could not be demonstrated as expected, consequently, the applicant was advised to perform adequate efficacy and safety studies for this product with results as stated above.

Clinical safety
A review of safety data of methylphenidate from data in literature is presented in the clinical overview. The results do not present any evidence that under medication with MR-formulations there are any changes in the risk profile of the substance.
The results of clinical studies with Medikinet retard are quite comparable to immediate release methylphenidate. The relevance of deviating incidences (gastrointestinal disorders) seems questionable due to the small patient numbers.

Bioequivalence
Comprehensive studies have been performed to show the bioequivalence of Medikinet retard taken one time a day versus an immediate release form taken two times a day and additionally to other MR formulations currently marketed. Therefore, Medikinet retard cannot be exchanged by other MR formulations currently marketed. A further result of these pharmacokinetic studies is the observation that the prolonged release principle of the capsules only works properly if it is taken with food.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION (SPECIFIC OBLIGATIONS, FOLLOW-UP MEASURES, IF APPLICABLE)

The risk/benefit ratio was considered positive and the application for Medikinet tablets and prolonged release capsules is approved.

After marketing authorisation the indication for *Medikinet retard 10 / 20 / 30 / 40 mg* (DE/H/0690/004-007/DC) was changed by a variation (see also INTRODUCTION), which was approved after referral on 17th November 2017 with the following obligation:

Proposed list of conditions pursuant to Article 22 a of Directive 2001/83/EC

- **Obligation to conduct post-authorisation measures in accordance with Article 22a of Directive 2001/83**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
A category 1 PASS with the following requirements - The study should be a non-interventional study in adult ADHD patients (aged ≥ 18 years). - The protocol should be submitted within 3 months after finalization of the referral procedure to PRAC. An updated RMP should be submitted along with this. - The design should be a prospective cohort study in different countries with a mean follow-up of 5 years. Interim reports should be provided yearly. - The following cardiovascular endpoints (in line with the ADDUCE study) should be studied: blood pressure, pulse rate, hypertension, left-ventricular hypertrophy, myocardial infarction and cardiomyopathy. - The psychiatric endpoints are to be determined. - A power calculation should be provided showing a sufficient sample size for these endpoints. - The final study report should be provided within 7 years after finalization of the referral procedure.	April 2018 (protocol submission) April 2025 (final study report)

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Update: 19th January 2018

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Medikinet retard 10 / 20 / 30 / 40 mg

Methylphenidate hydrochloride

DE/H/0690/001-007/MR

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
DE/H/0690/004-007/II/005	Results of Consultation with Target Patient Groups with update of PIL acc. to MRP-commitment	Yes	18.10.2007	Approved	
DE/H/0690/004-007/II/006	Update of ASMF of Orgamol	No	14.12.2007	Approved	
DE/H/0690/004-007/II/007	Update of ASMF of Orgamol	No	30.10.2007	Approved	
DE/H/0690/004-007/II/008	Change of SmPC section 4.3, 4.4, 4.6, 5.3 and PIL acc. to commitment of MRP	Yes	13.04.2008	Refused	
DE/H/0690/004-007/II/015	Update of product texts in diverse sections (for discussion of deviations of the Commission Decision for methylphenidate)	Yes	23.12.2009	Approved	
DE/H/0690/004-007/II/016	Submission of the User Test as well as the resulting leaflets following the Commission decision on the Article 31 Referral (22 June 2009) concerning methylphenidate containing products.	No	08.02.2010	Approved	
DE/H/0690/004-007/II/023	- based on two pivotal clinical studies with Medikinet retard for the treatment of adult ADHD, a clinical overview, which includes either these two clinical studies and the bibliographic data on methylphenidate-HCl, has been made in order to give an assessment of the benefit-risk ratio of Medikinet retard for the continuation of therapy in adulthood - inclusion of the possibility of treatment into the SmPC in section 4.2 (and 4.4 and 5.1.) using the same wording as it was granted for Concerta	Yes	04.10.2013	Approved	
DE/H/0690/004-010/II/035	B.II.b).4. d) Change in the batch size (including batch size ranges) of the finished product: The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes: Introduction of a second, increased batch size of the finished product: the batch size is doubled.	No	09.01.2015	Approved	
DE/H/0690/004-010/II/043/G	- To harmonize the text for the SmPC and PIL for the 5 mg capsules, the 10/20/30/40 mg capsules, and the 50/60 mg capsules. - To add the new initiation of treatment of ADHD in adults to the indication of the product.	Yes	17.11.2017	Approved	

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