

Decentralised Procedure
Public Assessment Report

Medikinet retard 50 mg
Medikinet retard 60 mg

Methylphenidate hydrochloride

DE/H/0690/009-010/DC

**Applicant: Medice Arzneimittel Plütter GmbH &
Co. KG**

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Medikinet retard 50 mg Medikinet retard 60 mg
INN (or common name) of the active substance(s):	Methylphenidate hydrochloride
Pharmaco-therapeutic group (ATC Code):	N06BA04
Pharmaceutical form(s) and strength(s):	Modified-release capsule, hard ; 50, 60 mg
Reference Number(s) for the Decentralised Procedure	DE/H/0690/009-010/DC
Reference Member State:	DE
Member States concerned:	AT, DK, ES, FI, LU, NL, NO, PL, SE, UK
Applicant (name and address)	Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37, D-58638 Iserlohn, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Medikinet retard 50 and Medikinet retard 60 mg*, is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behaviour disorders [...], is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

These decentralised applications consider a line-extension of the drug product “Medikinet retard” containing methylphenidate hydrochloride as drug substance (Article 10(3) hybrid application). The initial product strength (10-40 mg) were granted marketing authorisations in Germany on 29th December 2004 and 7th February 2006. The additional strengths of 5 mg has been introduced as line extension on 20.02.2008. The strengths actually applied for are 50 and 60 mg. With Germany as the Reference Member State in this Decentralised Procedure (DCP), the Marketing Authorisation Holder, Medice Arzneimittel Pütter GmbH & Co. KG, is applying for marketing authorisations for Medikinet retard 50 mg / 60 mg in AT, DK, ES, FI, LU, NL, NO, PL, SE, UK.

II.2 About the product

Medikinet retard consists of two fractions of methylphenidat hydrochloride as the active ingredient in a 1:1 ratio: immediate release pellets releasing the drug substance in the acidic stomach immediately after intake, and enteric coated pellets with sustained release at pH values above 6.8.

Methylphenidate is a mild CNS stimulant with more prominent effects on mental than on motor activities (ATC Code N06B A04, Methylphenidate, centrally acting sympathomimetics). Its mode of action in man is not completely understood but its effects are thought to be due to cortical stimulation and possibly to stimulation of the reticular activating system.

This biphasic retard formulation combines in a 1:1 ratio fast release and modified release methylphenidate in one capsule in order to achieve immediate plus extended drug release thus covering a standard school morning from around 8 am to 1 pm with a single dosage intake in the morning.

The benefit of drug which needs to be administered only once daily is apparent, especially for school-aged children.

The maximum single dose recommendation has been set to 60 mg (once a day) based on the outcome of clinical trials. However the highest strength of Medikinet Retard is actually 40 mg, what means that the maximum dose (if needed) could be achieved by administration of 2 tablets (2x30mg).

The additional benefit of Medikinet retard 50 and 60 mg capsules is the simplification of dosing, which can support or promote the compliance.

II.3 General comments on the submitted dossier

Clinical studies on Medikinet retard 10, 20, 30 and 40 mg were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that the products (immediate release tablets and modified release capsules) provide satisfactory clinical benefits.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance methylphenidate hydrochloride is described in the European Pharmacopoeia (Ph. Eur.). For the manufacturers of the active substance valid certificates of suitability of the EDQM have been submitted.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented.

Certificates of analysis for three consecutive batches of the strengths 60 resp. 50 mg capsules manufactured in August 2008 are provided. The batches are made from 30-60 mg immediate release pellets and enteric coated pellets batches which are of production scale. For this reason the batches are considered as production batches though the number of filled capsules is only 100.000 pieces. The data demonstrate good compliance with the release specification.

Stability studies have been performed on the same batches. The results presented show that all specified parameters are fulfilled under long term conditions up to 36 month and intermediate conditions for 6 month. Only a slight increase of the impurity content has been observed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

A shelf-life of 36 month for Methylphenidate hydrochloride 50 mg and 60 mg capsules packed in PVC/PVDC/Alu blisters is accepted. Because of the humid-sensitive pellets the storage recommendation is: "Keep in original container to protect the capsules from moisture" and „Do not store above 30 °C”.

III.2 Non-clinical aspects

Methylphenidate is a substance with well-known pharmacological and toxicological characteristics. This line extension applied for is lacking new nonclinical studies and a non-clinical overview. Reference has been made to Medikinet retard 5 mg, 10 mg, 20 mg, 30 mg and 40 mg (DE/H/0690/001-008). The applicant conducted two clinical bioequivalence studies for 60 mg Medikinet retard capsules (single- and multiple-dose study). C_{max} of the 60 mg test substance was shown to be almost identical to C_{max} of the reference substance 30 mg b.i.d. Therefore, it can be concluded that pharmacokinetics of Medikinet retard 50 and 60 mg are adequately covered by existing preclinical data of Medikinet retard 5 mg, 10 mg, 20 mg, 30 mg and 40 mg (DE/H/0690/001-008). From a non-clinical perspective, no new information is available, which would change the overall positive risk/benefit of the compound. The toxicologically relevant sections of the SmPC and PIL are in line with the previously accepted wording of the decentralized procedures DE/H/2222/001-003/DC and DE/H/2223/001-005/DC.

Environmental Risk Assessment (ERA)

Since Medikinet retard 50 and Medikinet retard 60 mg is intended for substitution of existing dosage strengths, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

The combination of inattentive, hyperactive, and impulsive behavior in children is recognized as a clinically relevant disorder if these behaviors are severe, developmentally inappropriate, and impair function at home and school. This kind of behavioral disorder is described in literature under a variety of names such as hyperkinesis, hyperkinetic syndrome, minimal brain dysfunction (MBD), attention deficit disorder with hyperactivity (ADDH) or attention deficit disorder (ADD) (Greenhill, 1989). Currently, two terms for this disorder are mainly used synonymously: attention deficit hyperactivity disorder (ADHD) or hyperkinetic disorder (HKD) (Swanson et al., 1998).

Methylphenidate is the best known and most widely used stimulant to treat ADHD in children (accounting for 70 % to more than 90 % of the ADHD drug therapy) while dexamphetamine and pemoline are generally regarded as second-line therapies (Patrick and Markowitz, 1997) while other therapeutic agents are under development (Horrigan, 2001).

Methylphenidat show a rather short halftime what makes it necessary to administer at least two doses per day. However, this dose regimen is uncomfortable for children as the second dosing time would fall in the regular school time. Therefore, the development of modified release dosage forms was initiated to help children over a school day with one single-dose in the morning.

A standard prolonged dosage form was anticipated to cause flat and constant plasma profiles probably leading to insufficient efficiency as methylphenidate is known to be effective in the ascending plasmalevels (acute tolerance).

Therefore, a biphasic dosage combining a fast and modified release fraction of the active substance form has been chosen, comparable to other available and approved long-acting methylphenidate formulations, like Metadate CD® or Equasym® XR (Anonymus, 2001). Another approved product, Concerta®, also follows a similar concept of combining fastrelease and modified-release properties in one drug (44; 45). Concerta® and Equasym® XR were approved in several European countries including Germany.

The maximum single dose recommendation has been set to 60 mg (once a day) based on the outcome of clinical trials. However the highest strength of Medikinet Retard is actually 40 mg, what means that the maximum dose (if needed) could be achieved by administration of 2 tablets (2x30mg).

The additional benefit of Medikinet retard 50 and 60 mg capsules is the simplification of dosing, which can support or promote the compliance.

Consequently the applicant has not performed additional clinical trials but performed bioequivalence studies to demonstrate the comparability of 60 mg vs 2x30 mg capsules.

Adult indication

Clinical studies for the adult indication had been provided by the applicant. Reference is made to the recently finalized variation DE/H/0690/004-007/II/023.

Pharmacokinetics

To support the application, the applicant has submitted as report the results of 2 bioequivalence studies to demonstrate the bioequivalence of the newly introduced 60 mg with the equivalent dose of the already authorised 30 mg strength.

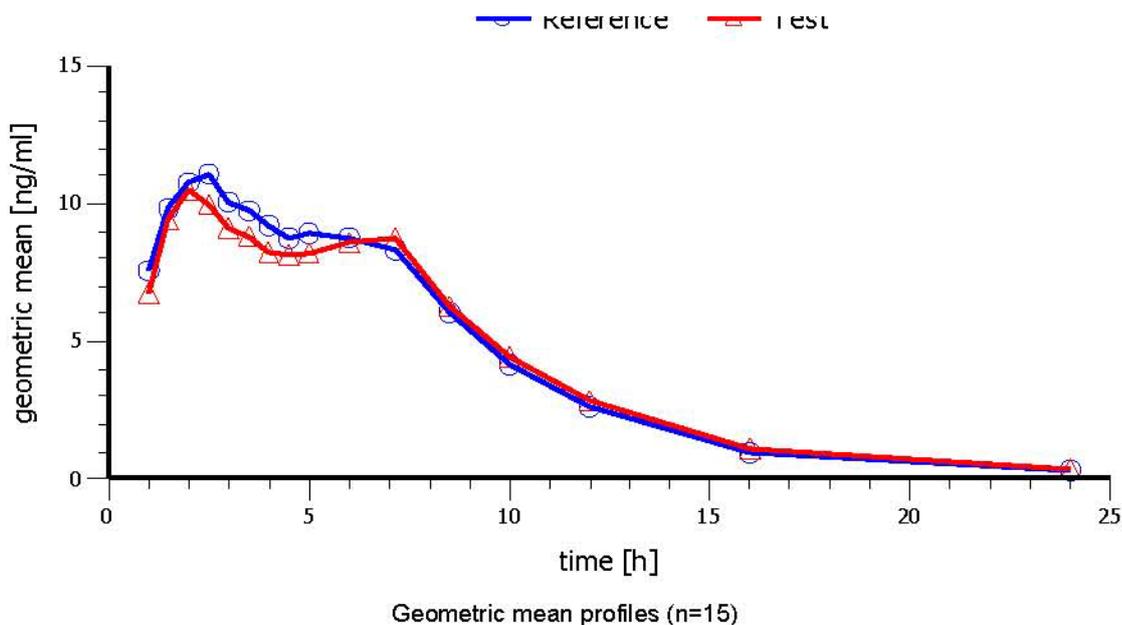
Study 1

A randomized, single-center, open-label, 2-way-crossover study in a two-stage design to investigate the comparative bioavailability of one capsule Medikinet® retard 60 mg (test) and two capsules Medikinet® retard 30 mg (reference) after single oral administration in 16 healthy male subjects. The study has been performed under fed conditions as the concomitant food intake is mandatory for this product. Regarding the standard pharmacokinetic variables bioequivalence has undisputably been shown. The results are rather robust and statistical analysis indicate no significant difference.

However, Medikinet retard is not standard dosage form. The capsules contain a fast releasing and a prolonged releasing fraction which lead to a biphasic plasma profile. The PKWP has recently released a Question & Answer Document (EMA/618604/2008/7) dealing with the requirements of establishing bioequivalence between biphasic modified release formulations. In summary it is recommended to show equivalence separately for both phases.

The advanced pharmacokinetic variables which reflect the biphasic drug liberation of the dosage form (e.g. AUC_{0-4} , AUC_{4-t} , $C_{max(0-4)}$ and $C_{max(4-t)}$) are, as although not prespecified, also well within conventional acceptance criteria.

Figure 1 Pharmacokinetic profile of 1x1 capsule of Medikinet retard 60 mg (test) and 1x2 capsules of Medikinet retard 30 mg (reference) after single oral administration (geometric means)

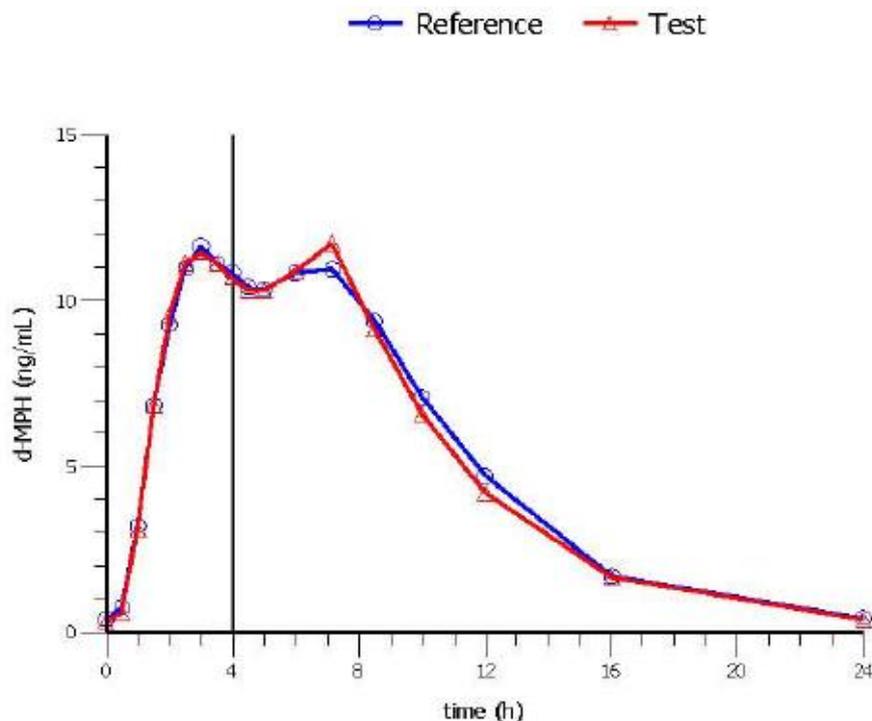


Study 2

The applicant has performed a multiple dose (4 days) study investigate the comparative bioavailability of one capsule Medikinet® retard 60 mg (test) and two capsules Medikinet® retard 30 mg (reference).

Again the bioequivalence could demonstrated for conventional pharmacokinetic variables as well for those which reflect the biphasic drug liberation of the dosage form (e.g. AUC_{0-4} , AUC_{4-t} , $C_{max(0-4)}$ and $C_{max(4-t)}$) as recommended by are, although not prespecified, well within conventional acceptance criteria. Question & Answer Document (EMA/618604/2008/7)

Figure 2 Pharmacokinetic profiles of 1x1 capsule of Medikinet retard 60 mg (test) and 1x2 capsules of Medikinet retard 30 mg (reference) after multiple oral administrations (geometric means)



Medikinet retard 50 mg

The applicant applies for strength biowaiver for the 50 mg strength and justifies this approach by the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/ 98 Rev. 1/ Corr) from Aug 1, 2010. Similarity of dissolution profiles could be demonstrated for a product range of 30 to 60 mg in different media for both dissolution phases.

The product applied for is not a standard immediate release dosage form as it also contains a prolonged release part. Therefore the Note for Guidance on modified release oral and transdermal dosage forms (CPMP/EWP/280/96 Corr.) should be considered as well. The document states a single dose study under fasting conditions on the highest strength is sufficient, provided that the compositions of the lower strengths are proportional to that of the highest strength, the formulations contain identical beads or pellets and the dissolution profiles are acceptable. As the pellets of the initial product strengths are qualitatively the same, the different strengths differ only by the amount of capsule filling and the other criteria cited in the guideline are fulfilled, a strength biowaiver is considered acceptable from regulatory point of view.

Additionally to the actually filed bioequivalence studies with the 60 mg strength the applicant has provided in the initial marketing authorisation bioavailability data of the 40 mg strength as well. In summary the provided data package allow a comparison across the studies which indicate that an interpolation of in vivo data is considered justified.

Pharmacodynamics

N/A

Clinical efficacy

N/A

Clinical safety

N/A

User Testing

The marketing application is a line-extension application concerning the already approved product line Medikinet retard 5 mg – 40 mg. Obviously there are minor changes to the PL referring to product name and composition of Medikinet retard 50 and 60 mg. Therefore, no new consultation with target patient groups was undertaken.

Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

Summary table of safety concerns

Important identified risks	Hypertension, tachycardia, Raynaud's phenomenon, hallucinations, psychosis/mania, anorexia, decreased rate of growth, aggression, depression
Important potential risks	Migraine, repetitive behaviours, QT prolongation, cyanosis, arrhythmias, sudden death, ischaemic cardiac events, cerebrovascular disorders, hostility, suicidality, tics / Tourette's syndrome / dystonias, effect on final height, sexual maturation delayed, carcinogenicity, lymphocytic leukemia, neonatal cardio-respiratory toxicity, neonatal effects on growth, diversion, off-label use, withdrawal syndrome, drug abuse / drug dependence
Important missing information	Long term use (cardiovascular, cerebrovascular, and psychiatric effects)

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important risks		
Raynaud's phenomenon (ident.) Migraine (pot.) Repetitive behaviours (pot.) QT prolongation (pot.) Cyanosis (pot.) Sexual maturation delayed (pot.) Carcinogenicity (pot.) Lymphocytic leukemia (pot.)	SmPCs: Refer to corresponding SmPC sections; prescription only medicine	None proposed
Important risks		
Hypertension (ident.) Tachycardia (ident.) Hallucinations (ident.) Psychosis/Mania (ident.) Aggression (ident.) Depression (ident.) Anorexia (ident.) Decreased rate of growth (ident.) Hostility (pot.) Tic (pot.) Tourette's syndrome (pot.)	SmPCs: Refer to corresponding SmPC sections; prescription only medicine	Educational tool (physician's guide to prescribing and checklists)

Dystonia (pot.) Arrhythmias (pot.) Sudden death (pot.) Ischaemic cardiac events (pot.) Cerebrovascular disorders (pot.) Suicidality (pot.) Effect on final height (pot.) Off-label use (pot.) Diversion (pot.) Withdrawal syndrome (pot.) Drug abuse (pot.) Drug dependence (pot.)		
Important potential risks		
Neonatal cardio-respiratory toxicity(pot.) Neonatal effects on growth(pot.)	SmPCs: Refer to corresponding SmPC sections;prescription only medicine; in addition, any not strictly needed drug use in pregnancy/lactation is avoided by health care professionals as well as patients.	None proposed
Important missing information		
Long term use	SmPCs: Refer to corresponding SmPC sections;prescription only medicine; in addition, any not strictly needed drug use is avoided by health care professionals as well as patients.	None proposed

A prescription guide is available.

Periodic Safety Update Report (PSUR)

Methylphenidate is subject to PSUR Work Sharing with the UK acting as P-RMS.

The DLP for the next PSUR is 10.10.2013 followed by yearly new PSURs.

Common renewal date

Likewise, renewal date should be synchronised with the applicant's other methylphenidate hydrochloride containing products. Therefore, renewal date of this medicinal product is 11.11.2018.

IV. BENEFIT RISK ASSESSMENT

The application concerns a line extension of an already marketed product series. As the new strengths are covered by the maximum dose of the already authorised product series it is considered acceptable that no new efficacy and safety studies have been conducted.

The bioequivalence between the 60 mg and the already marketed (2x) 30 mg strength has been undisputable shown. Even for the highest strength no relevant accumulation occurs.

For the 50 mg a strength biowaiver has been fully justified.

From a clinical point of view the benefit risk assessment is positive.

The application is approved.

For intermediate amendments see current product information.