# Mutual Recognition Procedure

# Public Assessment Report

# Medikinet retard 5 mg

# Methylphenidate hydrochloride

# DE/H/0690/008/MR

# Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

**This module reflects the scientific discussion for the approval of Medikinet retard 5 mg. The procedure was finalised on 9th December 2010. For information on changes after this date please refer to the module 'Update'.**

# TABLE OF CONTENTS

# ADMINISTRATIVE INFORMATION

| | |
|---|---|
| **Proposed name of the medicinal product in the RMS** | Medikinet retard 5 mg |
| **Name of the drug substance (INN name):** | Methylphenidate hydrochloride |
| **Pharmaco-therapeutic group (ATC Code):** | N06BA04 |
| **Pharmaceutical form(s) and strength(s):** | modified release capsules, hard; 5 mg |
| **Reference Number(s) for the Decentralised Procedure** | DE/H/0690/008/MR |
| **Reference Member State:** | DE |
| **Concerned Member States:** | AT, DK, ES, FI, LU, NL, NO, PL, SE, UK |
| **Applicant (name and address)** | MEDICE Arzneimittel Pütter GmbH & Co. KG<br>Kuhloweg 37<br>58638 Iserlohn<br>Germany |

# I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Medikinet retard 5 mg*, in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) (in children), is approved. A national marketing authorisation was granted on 20.02.2008.

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. EXECUTIVE SUMMARY

## II.1 Problem statement

These mutual recognition applications consider a generic version of methylphenidate hydrochloride.

The originator product is Ritalin Tablets (Marketing Authorisation Holder: Novartis Pharmaceuticals UK Limited).
The initial product strengths (10-40 mg) were granted marketing authorisations in Germany on 30th July 2003 and 29th December 2004 and the strengths actually applied were granted marketing authorisation as line extension on 20.02.2008.
With Germany as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, Medice Arzneimittel Pütter GmbH & Co. KG, is applying for marketing authorisations for Medikinet retard 5 mg in AT, DK, ES, FI, LU, NL, NO, PL, SE and UK.

## II.2 About the product

Medikinet retard consists of two fractions of methylphenidate 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 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 strength actually applied for is introduced to allow a more differentiated dosing within 5 mg steps.

The objective of the development programme was to formulate a robust, stable, acceptable formulation of Medikinet retard 5 mg comparable in performance to Ritalin Tablets, which are the reference product for this generic application. As the capsule content of the different strengths is strictly homothetic the development work is rather straightforward.

### II.3 General comments on the submitted dossier

The clinical dossier corresponds to the recently approved procedure DE/H/2223 DC and is found generally acceptable.

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

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.

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 prior to granting its national authorisation.
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 supplied by two different manufacturers. The manufacturer of the finished product established a comprehensive overall specification for the drug substance from the named sources. A Ph. Eur. monograph is available for methylphenidate hydrochloride and the drug substance of both manufacturers was shown to comply with it.
Although a CEP was granted for manufacturer A, for each manufacturer an EDMF / ASMF is submitted to which reference is made.
Suitable stability data has been presented for methylphenidate hydrochloride from the two manufacturers, supporting the individual re-test periods.

**Drug product**

Stability data on several pilot and production scaled batches (including data from other strengths) have been provided. Drug substance from the two manufacturers has been used for the stability batches.

Capsules: The results presented, show that all specified parameters are fulfilled during shelf-life under long term (25 °C / 60 % RH), and intermediate (30 °C /60 % RH) conditions, but the specification for the degradation products was not met at accelerated (40 °C / 75% RH) conditions. All data which are available so far indicate that the quality of the active substance from the different manufacturers has not any impact on the stability of the finished product. A shelf-life of 36 months, which is covered by long term stability data, with the storage recommendation ‘Do not store above 30°C’, due to impurity levels under accelerating conditions, is accepted.

### III.2 Non-clinical aspects

Methylphenidate is a substance with well-known pharmacological and toxicological characteristics. Non new studies were provided by the applicant but the non-clinical overview represents adequate reviews of published data. 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 SPC have been adapted to the Article 31 referral for methylphenidate-containing products (14th of July 2009). Section “Pregnancy and Breast-Feeding” in the PIL has been previously accepted to differ from the referral text in order to be more patient-friendly (decentralized procedure DE/H/2222/001-003/DC and DE/H/2223/001-005/DC).

## III.3 Clinical aspects

Medikinet retard 5 mg (modified release capsules) for the indication of attention deficit hyperactivity disorder (ADHD) are applied as hybrid applications to Ritalin 10 mg Tablets.
This 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.
Medikinet retard consists of two fractions of active substance 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.
The originator product, on which nearly all literature for ADHD is based, is Ritalin® (Novartis Pharma) and is therefore to be considered the adequate reference drug for bioavailability studies.

The in vivo properties of the medicinal product were investigated in 7 bioavailability studies and the efficacy and safety has been investigated in 2 clinical studies and 1 observational study.
In a retrospective view on the national and MRP procedure it can be concluded that the numerous clinical studies are caused by the intention of the applicant to waive for clinical efficacy studies if the bioequivalence can be shown between the modified release capsules and the immediate release tablets (bid) as reference.
The proof of bioequivalence could not be fully supplied. Efficacy studies were inevitable and referring to this, the applicant applied for a pre-application scientific advice.

Methylphenidate hydrochloride was first synthesized in 1944 and was introduced in clinical therapy in 1959. Thus experience from more than 50 years of non-clinical and clinical use is available and information for non-clinical and clinical documentation was obtained from standard text books and published scientific literature as well as several studies performed by Medice Arzneimittel.

With Concerta® Retardtabletten and Ritalin LA already other biphasic immediate/modified release formulation of methylphenidate are marketed in the EU, but the principle of substance release is different.

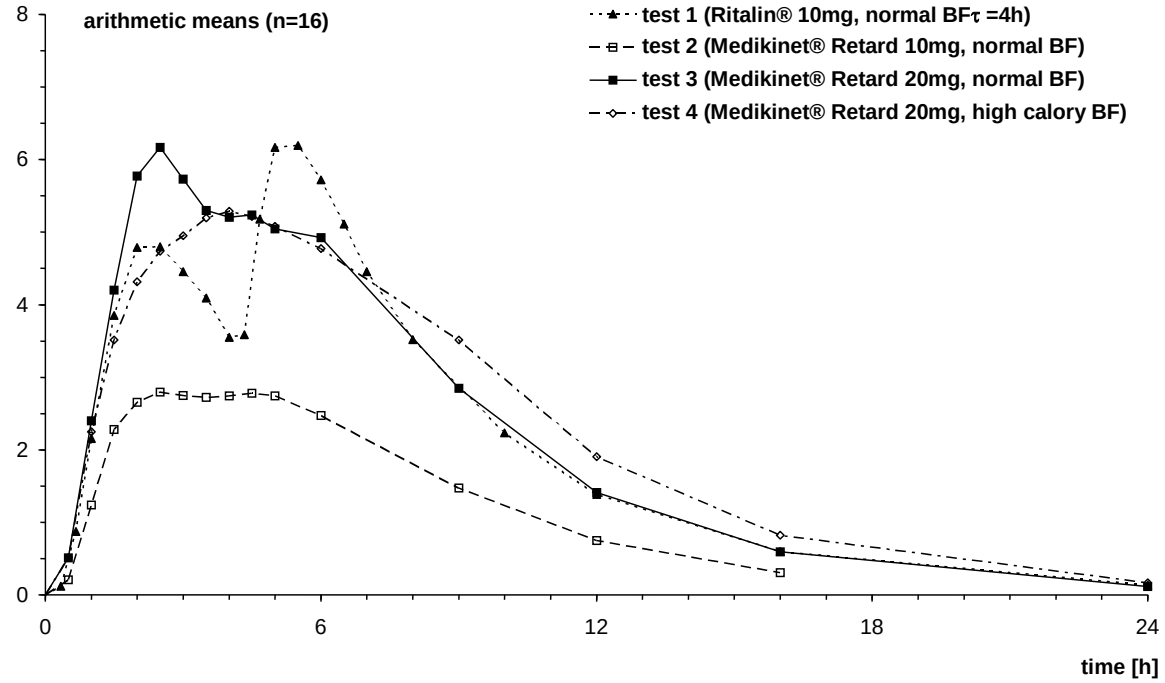
For the 5 mg strength the applicant applied for biowaiver for the following reasons:

- The 5 mg strength was developed as a line extender of MPH CR 10 mg
- The qualitative composition of both strengths is the same (homothetic)
- The new medicinal product only contains half the amounts of active substance and excipients
- The dissolutions profiles are similar under identical conditions
- In the bioequivalence studies dose linearity between 10-40 mg could be shown

**Pharmacokinetics**

Medikinet retard consists of two fractions of active substance 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.
Consequently MPH CR has a plasma profile showing two phases of active substance release, with an initial $C_{max}$ at 1-2 h comparable to the IR tables and the formation of a 3-4 hour plateau phase during which concentrations do not sink below 75 % of the peak plasma concentration. The amount of methylphenidate hydrochloride absorbed when administered once daily is do far comparable with conventional immediate-release formulations administered twice daily. However the plasma level course shows some differences e.g. under the IR therapy a clearly separated second peak occurs. Representative plasma levels are presented below:

**Plots of the mean whole blood levels of methylphenidate hydrochloride over the 24 hour sampling period (From Study No: 4550205)**




Due to the retarding principle the new modified release formulation only works out properly when taken with food. The modified drug release is primary pH dependent so it is necessary that stomach passage is slowed down by food.
Therefore children who show a severe anacidity of the stomach should not be treated with Medikinet retard.
This is adequately reflected by dose recommendation and contraindications stated in the PIL and SPC.

As dose proportionality could be established overall strengths between the 10 mg and the 40 mg Medikinet retard formulations, adequate clinical dosing is possible.

**Pharmacodynamics**
The pharmacodynamics of methylphenidate is well characterized. Methylphenidate has got a basic phenylethylamine structure which is common to psychostimulant agents, like amphetamines (Holmes, 1995; Kollins, 2001). Preclinical studies have shown that stimulants facilitate the catecholaminergic neurotransmission by blocking the re-uptake of the monoamines dopamine and norepinephrine into the presynaptic neuron and by increasing the release of these monoamines into the extraneuronal space (Wilens, 1992).

Recognizing that methylphenidate binds with high affinity to the dopamine transporter or uptake channel, it was proposed that this binding blocks the synaptic clearance of impulse-released dopamine, leading to prolonged postsynaptic neurochemical mediation.

**Clinical efficacy**

Modified release formulation:

The applicant has performed two GCP-compliant clinical trials, evaluating the efficacy and tolerability of Medikinet retard in children with ADHD and an additional observational study. Additionally the basic assessment on the efficacy of methylphenidate hydrochloride is in general based on bibliographic data. As methylphenidate hydrochloride is a very old, well known substance that is marketed since over 40 years, only few additional literature data are presented in Module 2.7. The majority of the bibliographic data are presented in Module 2.5.

Additionally to the bioequivalence studies (see chapter 2.5.3.1), two clinical trials (N° 6520 9979 -02 and N° 6520-9973-01) have been performed by the applicant with this new formulation. The basic assessment on the efficacy of methylphenidate in general is based on bibliographic data.

A further observational study confirms the finding of the pivotal studies.

From the evaluation of all the above mentioned data the clinical efficacy of methylphenidate in the treatment of ADHD can be summarised as follows:

- Methylphenidate diminishes typical behaviour symptoms in ADHD patients, including motor over-activity, impulsiveness and inattentiveness. A significant improvement of these symptoms is seen in children as well as in adolescents.
- In addition to the core symptoms of ADHD methylphenidate improves associated behaviours including on-task behaviour, academic performance and social function. Furthermore vigilance, cognitive impulsiveness, reaction time, short-term memory, and learning of verbal and non-verbal material are improved by methylphenidate in children with ADHD. These effects appear to be dose-dependent and cross-situational, including home, clinic and school.
- Methylphenidate is more effective than dexamphetamine or tricyclic antidepressants in the overall treatment of ADHD.
- Short-term efficacy of methylphenidate in children with ADHD is well documented in literature, whereas the benefits and risks of extended methylphenidate treatment are not fully understood.
- Methylphenidate responsiveness may be affected by comorbid disorders, as e.g. anxiety disorder.
- The effectiveness of methylphenidate is independent from the formulation as IR or SR-application.
- The rationale for the use of SR-application is mainly a practical one avoiding the need of re-dosing during school day which often is not feasible as it is not possible to delegate drug dispensing to the teacher.
- MPH CR once a day reduces ADHD symptoms significantly compared to placebo. The therapeutic efficacy is quite comparable to fast release methylphenidate twice a day (67; 68). Some deterioration may be seen in the afternoon compared to fast release methylphenidate twice a day.
- MPH CR (capsules) is only suitable for patients already titrated to their efficacy dose, therefore a fast release methylphenidate has to be used in the beginning of methylphenidate drug therapy (during titration).
- For adequate efficacy of MPH CR it is essential that it is taken together with food in order to slow down the stomach passage so that the enteric coated pellets reach the duodenum with a time lack of 3 - 4 h.

**Clinical safety**

The safety profile of methylphenidate is well established in literature and can also be derived from the authorised SPCs of Ritalin and other approved products. As the comparative bioavailability of Medikinet retard and Ritalin IR clearly demonstrates the accumulation does not happen and plasma levels are cleared after 24h the safety profile of the modified release formulation should not differ from that of the immediate release preparations.

The safety profile of methylphenidate indicates a positive risk/benefit ratio and methylphenidate can therefore be considered as an effective and safe drug in the symptomatic treatment of ADHD.

**Legal Status**
Medicinal product is subject to special and restricted medical prescription.

**User Testing**
In order to meet the requirements of Directive 2004/27/EC, a readability test was performed on the strengths initially applied for by Dr. Luckow & Associates in 2007. The testing place was Ulm, Germany.

The user test was carried out with Parents, preferentially those with children suffering of ADHD. The test was about the package leaflet of Medikinet tablets and of Medikinet Retard. The different strengths have been summarised in common PILs. The test consisted of 14 questions about the content of the leaflet of both drug products and 3 additional questions dealing with issues of the sustained release capsule.
The testing was performed on 30 volunteers and was done in two rounds.

The first test round (total n=10) indicated that, for each question, at least 85.9% of all questions were correctly reported. 11.2% of the questions the subjects failed to give correct answers.
Therefore the texts have been revised.
In the second round (n=20) the subjects could successfully locate and interpret the information for 99.7 % of all questions.

As this procedure can be considered as line extension, bridging of the data is fully justified.

**Summary Pharmacovigilance system**
Details have been provided of the Medice pharmacovigilance system. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**
The risk management plan was found acceptable.

# IV. BENEFIT RISK ASSESSMENT
Based on the review of the data on quality, safety and efficacy, the application for *Medikinet retard 5 mg*, in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) (in children), is approved.

After marketing authorisation the indication 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 21a 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<br>- The study should be a non-interventional study in adult ADHD patients (aged ≥ 18 years).<br>- 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.<br>- 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.<br>- 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.<br>- The psychiatric endpoints are to be determined.<br>- A power calculation should be provided showing a sufficient sample size for these endpoints.<br>- The final study report should be provided within 7 years after finalization of the referral procedure. | April 2018 (protocol submission)<br><br>April 2025 (final study report) |

# Public Assessment Report

# Update: 19th January 2018

# Medikinet retard 5 mg

# Methylphenidate hydrochloride

# DE/H/0690/008/MR

# Applicant: Medice Arzneimittel Pütter GmbH & Co. KG

**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/0690/004-010/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:<br>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.<br>- 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)