LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Ritalin
(methylphenidate hydrochloride)

Asp no : 2013-1330

This module reflects the scientific discussion for the approval of Ritalin. The procedure was finalised at 2014-10-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Novartis Sverige AB has applied for a marketing authorisation for Ritalin, 60 mg modified-release capsule. The active substance methylphenidate hydrochloride is the same as in Ritalin, 10 mg, 20 mg, 30 mg, and 40 mg, modified-release capsules, marketed by Novartis Sverige AB since 2005. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Ritalin 60 mg is presented in the form of capsules containing 60 mg of methylphenidate hydrochloride. The excipients are sugar spheres (sucrose, maize starch, starch hydrolysates), ammonio methacrylate copolymer type B, methacrylic acid-methyl methacrylate copolymer 1:1 (Methacrylic acid copolymer type A), talc, triethyl citrate, macrogol, titanium dioxide, gelatine, black iron oxide, red iron oxide, yellow iron oxide, shellac , propylene glycol and potassium hydroxide. The capsules are filled with immediate (IR) and delayed release (DR) beads and packed in high density polyethylene (HDPE) bottles with child resistant polypropylene (PP) closures with an aluminium induction seal.

II.2 Drug Substance

Methylphenidate hydrochloride has a monograph in the Ph Eur.

Methylphenidate hydrochloride is a white, crystalline powder which is *freely* soluble in water. The structure of methylphenidate hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Ritalin 60 mg hard modified-release capsule is formulated using excipients described in the current Ph Eur, except for the colorants iron oxides which comply with e.g. NF and directive 2008/128/EC. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01). The gelatine of the capsule shells is of animal origin and copies of eight TSE-certificates of suitability for the gelatine used by the capsule manufacturer are presented.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30 °C.

III. 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 Introduction

Ritalin 60 mg hard modified-release capsule is intended for use in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Currently, Ritalin is available as 10 mg, 20 mg, 30 mg and 40 mg strengths. A new 60 mg strength for Ritalin modified-release capsule is proposed, which is intended to avoid the need for taking two capsules to achieve a 60 mg daily dose.

IV.2 Pharmacokinetics

Methylphenidate is a well-known substance that has been used for many years in the European Union. There are currently four strengths approved of Ritalin modified-release capsules: 10 mg, 20 mg, 30 mg and 40 mg and also an immediate-release formulation of 10 mg. The current line extension concerns the addition of a new strength of 60 mg to the modified-release version of the formulation.

Methylphenidate (MPH) is readily absorbed from the gastrointestinal tract. Protein binding is low. The plasma elimination half-life is about 2 hours. MPH is excreted as metabolites mainly in the urine with small amounts appearing in the faeces; less than 1% appears in the urine as unchanged MPH. MPH undergoes extensive first-pass metabolism. The major metabolite is ritalinic acid (2-phenyl-2-piperidyl acetic acid). Ritalin is a racemic mixture of the d- and l-enantiomers of MPH, where the d-enantiomer is more pharmacologically active than the l-enantiomer. Data from previous studies indicate that linear pharmacokinetics prevails up to at least 20 mg.

The Ritalin modified-release formulation consists of a hard gelatine capsule containing a mixture of immediate release (IR) and delayed release (DR) beads.

The new 60 mg capsule is intended to avoid the need for taking two capsules of 30 mg to achieve the approved dose of 60 mg. The Ritalin 60 mg modified-release capsule is manufactured using the same mixture of IR and DR beads that are used for the approved 10 mg, 20 mg, 30 mg and 40 mg strengths. The fill weight has been adjusted proportionally to obtain the new 60 mg capsule.

Given that the new 60 mg strength is a proportional upscale of the 30 mg strength and that the 60 mg dose is already approved, no further studies are needed from a pharmacokinetic point of view.

IV.3 Pharmacodynamics

Methylphenidate is a central nervous system stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

IV.4 Clinical efficacy

No additional clinical studies have been carried out specifically to support the efficacy of Ritalin 60 mg modified-release capsule strength, but the efficacy of Ritalin modified-release capsule at 60 mg dose has been evaluated previously in a Phase III efficacy and safety study RIT124D2302 and its 6-month extension RIT124D2302E1. In these studies the 60mg dose strength was achieved by a combination of 2x30 mg Ritalin capsules, as has been the case in clinical practice. The results of study RIT124D2302 were submitted in a separate variation application to extend the indication of Ritalin modified release capsules to include the adult ADHD population.

IV.5 Clinical safety

No clinical studies have been performed for the current application to specifically support the safety of Ritalin 60 mg modified-release capsule. However, the safety of Ritalin modified-release capsule at 60 mg dose has been evaluated in a Phase III efficacy and safety study RIT124D2302 and its 6-month extension RIT124D2302E1. The results of the pivotal study RIT124D2302 were submitted in a separate variation application to extend the indication of Ritalin modified release capsules to include the adult ADHD population. The 60 mg dose strength was achieved by a combination of 2x30 mg Ritalin capsules.

IV.6 Discussion on the clinical aspects

Ritalin 60 mg hard modified-release capsule is intended for use in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Currently, Ritalin is available as 10 mg, 20 mg, 30 mg and 40 mg strengths. The new 60 mg strength for Ritalin modified release capsule is proposed to avoid the need for taking two capsules 30 mg to achieve a 60 mg daily dose. Although no additional clinical studies have been carried out specifically to support the 60 mg capsule strength, the safety and efficacy of Ritalin modified release capsules at 60 mg dose was further evaluated in a Phase III efficacy and safety study RIT124D2302 and its 6-month extension RIT124D2302E1. The results of the pivotal study RIT124D2302 were submitted in a separate variation application to extend the indication of Ritalin modified release capsules to include the adult ADHD population.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

MPA is of the opinion that a full user test was not required since the leaflet is harmonised after referral.

VI. APPROVAL

Ritalin, 60 mg modified release capsule was approved in the national procedure on 2014-10-09.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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