LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zatrispec
(rizatriptan benzoate)

SE/H/1246/01-03/DC

This module reflects the scientific discussion for the approval of Zatrispec. The procedure was finalised at 2012-11-08. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Vaia S.A. has applied for a marketing authorisation for Zatrispec, tablets, 5 and 10 mg and orodispersible tablets, 10 mg, claiming essential similarity to Maxalt, tablet, 5 mg and 10 mg and Maxalt Rapitab, orodispersible tablet, 10 mg marketed in Sweden by Merck, Sharp & Dohme B.V. The product contains rizatriptan benzoate as active substance. For approved indications see the Summary of Product Characteristics. The reference products used in the bio-equivalence studies are Maxalt, tablets, 10 mg and Maxalt Melt, Oral Lyophilisates, 10mg marketed by Merck Sharp & Dohme Limited in the UK.

II. QUALITY ASPECTS

II.1 Introduction

Zatrispec is presented in the form of tablets and orodispersible tablets containing either 5 mg or 10 mg of rizatriptan (in the form of rizatriptan benzoate). The excipients for the tablets are mannitol, sorbitol, crospovidone, red iron oxide, colloidal anhydrous silica and magnesium stearate. The excipients for the orodispersible tablets are mannitol, sorbitol, crospovidone, saccharin sodium, peppermint flavour, colloidal anhydrous silica and magnesium stearate. The tablets and orodispersible tablets are packed in OPA/Aluminium/PVC/aluminium blister.

II.2 Drug Substance

Rizatriptan benzoate has a monograph in the Ph Eur.

Rizatriptan benzoate is a white or off-white crystalline powder which is soluble in water. The structure of rizatriptan benzoate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and 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

Zatrispec is formulated using excipients described in the current Ph Eur, except for red iron oxide and peppermint flavour which are controlled according to USP/NF monograph (red iron oxide) and acceptable in house specifications (peppermint flavour). All raw materials used in the product are of vegetable origin or 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 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. For the tablets no storage restriction is required. The oro-dispersible tablets should be kept in the original package in order to protect from moisture.

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

Rizatriptan has an oral bioavailability of 40-45 %. Following an oral dose of rizatriptan tablets maximal plasma concentrations occur at approximately 1-1.5 hours. With orodispersible tablets, the time to maximal plasma concentration is delayed 30-60 minutes compared to tablets. Intake with food did not affect the degree of absorption for rizatriptan tablets, but the absorption was delayed by approximately one hour. Intake with food has not been studied for the orodispersible tablets, but a further delay in the absorption of rizatriptan may occur when the orodispersible tablets are administered after meals. There are no restrictions with respect to food in the SPC of the originator, except for a statement that the effect may be delayed in case of intake with food. The SPC states that AUC increases near-proportionally with dose over a dose range of 2.5-10 mg following oral administration. According to a study by Lee et al (1999) the difference in dose-adjusted AUC between 5 and 10 mg was less than 25%, and thus the pharmacokinetics of rizatriptan is considered to be linear between 5 and 10 mg. The terminal half-life is 2-3 hours.

Two bioequivalence studies have been submitted, one for the tablets and one for the orodispersible tablets.

Tablets

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 44 healthy volunteers, comparing Rizatriptan, 10 mg, tablets, manufactured by Arrow Malta on behalf of Cobalt Pharmaceuticals Company with Maxalt, 10 mg, tablets under fasting conditions. The study was conducted at Algorithme Pharma Inc., Mount-Royal, Quebec, Canada between 10th and 18th July 2011. Blood samples were collected pre-dose and up to 12

hours post-dose. The study design is considered acceptable. Plasma concentrations of rizatriptan were determined with an adequately validated LC/MS/MS method. 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%. The difference in t_{max} (0.69 h for test, 0.75 h for reference) was not statistically significant. From a pharmacokinetic point of view, absence of studies with the additional strength 5 mg is acceptable, as the pharmacokinetics of rizatriptan is linear between 5 mg and 10 mg.

Orodispersible tablets
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Rizatriptan 10 mg orally disintegrating tablet, manufactured by Arrow Malta on behalf of Cobalt Pharmaceuticals Company with Maxalt Melt, 10 mg, oral lyophilisate under fasting conditions. The study was conducted at Algorithme Pharma Inc., Mount-Royal, Quebec, Canada between 22nd May and 20th June 2011. Blood samples were collected pre-dose and up to 12 hours post-dose. The study design is considered acceptable. Plasma concentrations of rizatriptan were determined with an adequately validated LC/MS/MS method. 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%. The median t_{max} was the same for test and reference formulation (1.25 hours).

Based on the submitted bioequivalence studies, Zatrispec tablets and orodispersible tablets are considered bioequivalent with Maxalt/Maxalt Rapitab.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of:

1. A bridging report making reference to Zolmitriptan film-coated tablets, DK/H/1956-62/001-004/DC and Sumatriptan tablets, UK national procedure PL 18909/0168-0002. The bridging report submitted by the applicant has been found acceptable.
2. A user consultation study (focus test) in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The results of the conducted bioequivalence studies can be extrapolated to the other strength 5mg, since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

The risk/benefit ratio is considered positive and Zatrispec, tablets, 5 and 10 mg and orodispersible tablets, 10 mg, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Zatrispec, tablets, 5 and 10 mg and orodispersible tablets, 10 mg, was successfully finalised on 2012-11-08.

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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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
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