LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Omeprazol Pensa
(omeprazole)

SE/H/1034/01-03/MR

This module reflects the scientific discussion for the approval of Omeprazol Pensa. The product was authorised in April 28th 2011. 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

Pensa Pharma AB, Sweden has applied for a marketing authorisation for Omeprazol Pensa gastro-resistant capsules, hard, 10 mg, 20 mg and 40 mg claiming essential similarity to Losec, gastro-resistant tablets, 10 mg, 20 mg and 40 mg marketed in Sweden by AstraZeneca. The product contains omeprazole as active substance. For approved indications see the Summary of Product Characteristics. The reference products used in the bio-equivalence study are Antra 10 mg capsules manufactured by Astra GmbH, Germany; Mopral 20 mg capsules manufactured by Laboratorio Astra España S.A., Spain; Antra MUPS 20 mg tablets manufactured by Astra GmbH, Germany and Antra 40 mg capsules manufactured by Astra GmbH, Germany.

II. QUALITY ASPECTS

II.1 Introduction

Omeprazol Pensa is presented in the form of capsules containing 10, 20 and 40 mg, respectively, of omeprazole. The excipients are hypromellose, talc, titanium dioxide, methacrylic acid-ethyl acrylate copolymer, triethylcitrate, maize starch, sucrose, gelatin, shellac, propylene glycol, ammonium hydroxide, potassium hydroxide and black iron oxide. The capsules are packed in Al/Al-blisters or HDPE bottles.

II.2 Drug Substance

Omeprazole has a monograph in the Ph Eur.

Omeprazole is a white or almost white, crystalline powder which is very slightly soluble in water. The structure of omeprazole has been adequately proven and its physico-chemical properties sufficiently described. 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

Omeprazol Pensa gastro-resistant capsules, hard, are formulated using excipients described in the current Ph Eur, except for the ingredients of the printing ink, which are described in the USP. 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 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 25° C.

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

Omeprazole is absorbed in the duodenum and the bioavailability is around 60%. Plasma protein binding is 95% and the volume of distribution 0.3 l/kg. The drug is metabolized in the liver by CYP2C19 and CYP3A4 to inactive metabolites, and 80% of the metabolites are excreted in urine.

The pharmacokinetics of omeprazole is not completely linear as the drug inhibits its own metabolism due to saturation of the 2C19 enzyme. Both first-pass and systemic metabolism are affected. However, during single-dose administration the non-linearity is modest and the main effect is observed during multiple-dose conditions.

A total of seven bioequivalence studies were submitted in support of the application. In the studies two different reference products were used; Mopral capsule and Antra MUPS. Both reference products are valid in the assessment of bioequivalence.

All single-dose bioequivalence studies were performed with the 20 mg strength. As the only difference between the strengths is the amount of gastro-resistant pellets filled in the capsules, the pharmacokinetic behaviour is expected to be similar for the other strengths. A bioequivalence study on the 20 mg tablet is therefore considered sufficient and the other strengths of 10 mg and 40 mg could be waived.

Bioequivalence for Cmax and AUC, within the conventional acceptance limits of 80-125%, was demonstrated after single-dose administration both under fasting and fed conditions using Mopral 20 mg tablets as the reference product and for AUC when Antra MUPS 20 mg capsules was used as reference product. In the study with Antra MUPS 20 mg the 90% CI for Cmax was however slightly outside the conventional 80-125% acceptance range under fasting conditions, but within the widened acceptance range of 75-133%, which were acceptable according to the old bioequivalence guideline, valid at the time of first approval. Also in the

fed state the 90% CI was outside the conventional acceptance range due to a lower food-effect of the test product compared Antra MUPS, which was also acceptable at the time of first approval. Based on the total information it is considered that bioequivalence has been sufficiently demonstrated.

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 a bridging report on the content making reference to Omeprazole Bluefish, IE/H/172/01/MR. The bridging report submitted by the applicant has been found acceptable.
The lay-out of the PIL has been tested separately and has been found acceptable.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Omeprazol Pensa gastro-resistant capsules, hard, 10 mg, 20 mg and 40 mg are recommended for approval.

VI. APPROVAL

Omeprazol Pensa, 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard, was approved in the national procedure in Sweden on 2009-12-11. The mutual recognition procedure for Omeprazol Pensa was successfully finalised on 2011-04-28.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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
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