IPAR

Public Assessment Report

Scientific discussion

IE/H/172-183/1-3
IE/H/184/1-2

Omeprazole Bentley 10mg, 20 mg and 40 mg capsules
Mylcer 10, 20 & 40 mg capsules
Losapol 10, 20 & 40 mg capsules
Soothome 10, 20 & 40 mg capsules
Lemowan 10, 20 & 40 mg capsules
Kalgriff 10, 20 & 40 mg capsules
Hentom 10, 20 & 40 mg capsules
Tumelin 10, 20 & 40 mg capsules
Bentome 10, 20 & 40 mg capsules
Omeprazole Teva Pharma 10, 20 & 40 mg capsules
Davliet 10, 20 & 40 mg capsules
Vomlez 10, 20 & 40 mg capsules
Pugritex 10, 20 mg capsules
(Omeprazole)

This module reflects the scientific discussion for the approval of Omeprazole.
The procedure was finalised at < day 90 -23/10/2007 >. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

The Public Assessment Report (PAR) reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for granting a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information.
The legal basis for the PAR is contained in Article 21 of EC Directive 2001/83, as amended by Directive 2004/27/EC. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.
Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Omeprazole 10mg, 20mg and 40mg Capsules from Bentley Pharmaceuticals Limited. The procedures involved the following countries:

IE/H/172/1-3 Denmark, Finland, Germany, Norway, Sweden
IE/H/180/1-3 Poland
IE/H/181/1-3 Czech Republic, Germany, Poland and Slovakia
IE/H/184/1-2 Italy
IE/H/173-179 & 182-183/1-3 Germany

The Indications for Omeprazole are:

- Duodenal ulcers
- Benign gastric ulcers
- Reflux oesophagitis
- Maintenance treatment of reflux oesophagitis to prevent relapse
- Zollinger-Ellison syndrome
- Treatment of NSAID (Non Steroid Anti Inflammatory Drug) related gastric and duodenal ulcers
- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
- Symptomatic treatment of gastrooesophageal reflux disease
- In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori in patients with Helicobacter pylori associated peptic ulcers (see 4.2 Posology and method of administration)

The marketing authorization in Ireland is granted based on article 10(3) formerly 10.1 (a) (iii) of Directive 2001/83EEC, as amended). It concerns a generic application claiming essential similarity with the innovator product, Losec* Tablets (*In Ireland called Losec Mups). A study demonstrating bioequivalence with this innovator has been provided.

Names of the product: (multiple applications/duplicates)
Omeprazole Bentley 10mg, 20 mg and 40 mg capsules
Mylcer 10, 20 & 40 mg capsules
Losapol 10, 20 & 40 mg capsules
Soothome 10, 20 & 40 mg capsules
Lemowan 10, 20 & 40 mg capsules
Kalgriff 10, 20 & 40 mg capsules
Hentom 10, 20 & 40 mg capsules
Tumelin 10, 20 & 40 mg capsules
Bentome 10, 20 & 40 mg capsules
Omeprazole Teva Pharma 10, 20 & 40 mg capsules
Davliet 10, 20 & 40 mg capsules
Vomlez 10, 20 & 40 mg capsules
Pugritex 10, 20 mg capsules

RMS: Ireland

CMS:

IE/H/172/1-3 Denmark, Finland, Germany, Norway, Sweden
IE/H/180/1-3 Poland
IE/H/181/1-3 Czech Republic, Germany, Poland and Slovakia
IE/H/184/1-2 Italy
IE/H/173-179 & 182-183/1-3 Germany
Scientific advice given to applicant: No
EU Referral: No
Prescription status: prescription-only medicine
Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors ATC-code: A02B C01

Pharmaceutical form and strength(s): Capsules, hard, with gastro-resistant granules.

IE/H/172-183/01-03 = 10mg, 20mg and 40mg strengths.
IE/H/184/01-02 = 10mg and 20mg strengths.

Packaging : HDPE bottle and polypropylene cap with integral silica gel dessicant.

Pack sizes:
IE/H/172-183/01-03 = 5, 7, 14, 15, 20, 21, 28, 30, 42, 50, 56, 60, 84, 98, 100 or 500 Capsules
IE/H/184/01-02 = 14 Capsules

Mode of action: gastric proton pump inhibitor.
Approved indications and dosage
(see full SPC for details)

The Indications for Omeprazole are:

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- Benign gastric ulcers
- Reflux oesophagitis
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- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
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Date of first authorisation : 01/06/2007
Marketing Authorisation Number(s) (PA) :
PA 1284/2-13/1-3
PA 1284/14/1-2
Date of Public assessment report: 21/12/2007

Name and address of the authorisation holder :
Bentley Pharmaceuticals Ltd
25/28 North Wall Quay
Dublin 1
Ireland

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Omeprazole belongs to a class of substituted benzimidazoles that do not exhibit anticholinergic or H2 histamine antagonistic effects but reversibly suppress gastric acid secretion by inhibiting the enzyme H+K+-ATPase at the secretory surface of the gastric parietal cell. This enzyme system is considered as the acid (proton) pump and is responsible for the final step in gastric acid secretion. Omeprazole capsules are a controlled-release preparation.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The products were granted marketing authorisations in Ireland on 1st June 2007. With Ireland as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Bentley Pharmaceuticals Ireland Limited) gained approval for marketing authorisations in Germany, Sweden, Poland, Norway, Czech Republic, Slovakia, Italy, Finland and Denmark (see above).

During the procedure, potential serious risks to public health concerns were raised by two CMS.

Procedure; IE/H/184/01-02

Italy raised a potential serious risk to public health in relation to section 4.3 of the SPC.

Combination therapy with clarithromycin should not be used in heapatic impairment was deleted from the SPC.

Procedure IE/H/172/01-03

Denmark raised serious potential risks to public health on pack sizes for 10mg strength. It was agreed that this issues was a national issue and Denmark agreed it would discuss the issue with the applicant following the procedure.

Minor issues in relation to the SPC and patient leaflet were also raised by some of the concerned member states- all issues were satisfactorily resolved.

II QUALITY ASPECTS

II.1 Introduction

These applications are a copy of a capsule originally developed and marketed exclusively by AstraZeneca until the patent for it expired.
These products are very similar to the original product in composition and have been found in the quality assessment to have been made and controlled according to established international quality requirements.

II.2 Drug Substance

The active substance is omeprazole, an established active substance, which is certified to have been manufactured in accordance with the principles of Good Manufacturing Practice (GMP), i.e. worldwide standards.
Omeprazole is controlled according to European Pharmacopoeia (Ph. Eur.) requirements, which is reflected in the issue Certificate of Suitability (CEP).
The CEP also vouches for adequate stability of the active substance under defined conditions covering the period of tim during which the active substance may be used in the manufacture of the medical product.

II.3 Medicinal Product

P1. Composition
The dosage form is a capsule in three strengths:
10mg – red/orange capsule marked "010"
20mg – blue/orange capsule marked "020"
40mg – blue/orange capsule marked "040"
containing white to beige micro pellets.
The capsules contain: 10, 20 or 40mg, respectively, of the active substance 'omeprazole' together with the following oth ingredients allowing for the manufacture of granules :
Sugar spheres
Sodium starch glycolate,
Sodium laurilsulphate,
Povidone K-30,
Potassium oleate
Hypromellose,
Methacrylic acid-ethyl acrylate copolymer
Triethyl citrate,
Titanium dioxide
Talc
Capsule cap:
Erythrosine (10mg, 20, 40mg)
Indigo-carmine (20, 40mg only)
Red iron oxide (10mg only)
Titanium dioxide,
Gelatin
Capsule body:
Erythrosine
Quinoline yellow
Titanium dioxide
Gelatin
Printing ink consisting of shellac, ethanol, isopropyl alcohol, propylene glycol, n-butyl alcohol, polyvinyl pyrrolidone, sodium hydroxide and titanium dioxide.

The capsules are packed into plastic containers, containing a sachet of silica gel that retains any moisture in the product.

P2. Pharmaceutical Development
The drug product, a capsule, is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The purpose was to develop a product that is shown to be bioequivalent to the original brand leader Losec Mups, manufactured by AstraZeneca.

This was done in what is known as a 'bioequivalence study' where Losec Tablets, were compared to this drug product. A result both products are deemed to achieve the same desired action in the body.
Comparative dissolution data have also been provided.

P.3 Manufacture of the product

The product is manufactured in accordance with principles of Good Manufacturing Practice (GMP). The manufacturing process has been validated according to relevant European, and indeed, world-wide guidelines.

P.4 Control of Excipients
All ingredients in the capsule and the pellets comply with Ph. Eur. specifications.

P.5 Control of drug product
The control tests carried out on the final product are consistent with what would be expected for a capsule and ensure th is adequately manufactured. The test methods themselves have been assessed so that one can be confident that they will reliable results.
Data from three manufacturing campaigns have been presented, which show that the process will produce the same proc every time.

P.6 Packaging material
The packaging materials are bottles made of high density polyethylene (HDPE) and polypropylene (PP) caps with integ silica gel desiccant. This type of packaging complies with international requirements (Ph. Eur.).

P.7 Container closure system
Stability data of the finished product in the packaging indicated in P.6 have been provided in accordance with EU guide requirements. This has shown that the capsules can be stored for up to 3 years under storage conditions, 'Do not store at 30ºC. Keep the bottle tightly closed. Store in the original package.'

III NON-CLINICAL ASPECTS

These applications for a generic product claim essential similarity to Omeprazole (Astrazeneca Ltd), which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report, summarising relevant non-clinical studies has been included in the MR dossier; this was deemed satisfactory.

IV CLINICAL ASPECTS

The Applicant has provided 3 Bioequivalence studies in support for Bioequivalence of the test Omeprazole versus Omeprazole Reference Astrazeneca.

First Study
A multiple dose, randomised, balanced 2 period cross over design preceded or followed by a two period randomised balanced single dose crossover of Test Omeprazole 20mg administered with food.

36 Volunteers completed the study

Day 1 single dose fasting

	Point estimate %	90% confidence intervals	Coefficient of Variance %
C max	81.80	71.65-93.39	34.18
AUC_{o-t}	91.46	83.72-99.92	22.47
$AUC_{0-INFINITY}$	91.82	84.03-100.32	22.50

Day 5 steady state fasting

	Point estimate %	90% confidence intervals	Coefficient of Variance %
C max	89.91	80.69-100.19	27.66

AUC_{ss}	97.61	91.99-103.58	14.97

Single dose with high fat meal

	Point estimate %	90% confidence intervals	Coefficient of Variance %
C max	102.57	80.70-130.36	66.03
AUC_{o-t}	87.11	75.32-100.74	36.53
$AUC_{0-INFINITY}$	89.33	77.23-103.33	35.94

Second study

A second study consisted of a multiple dose, randomised balanced 2 period cross over with a washout 7 days between each dosing period. The final dose in each period was given after a standard breakfast.

36 Volunteers completed the study

Day 5 post food

	Point estimate %	90% confidence intervals	Coefficient of Variance %
C max	120.30	109.08-132.67	24.17
AUC_{o-t}	98.65	92.99-104.64	14.43
$AUC_{0-INFINITY}$	98.87	93.37-104.69	13.99

Third study

The study aimed to evaluate the pharmacokinetics of Omeprazole test 20 mg capsules versus Losec 20mg as reference after a high fat meal in healthy volunteers in a repeated dose, randomised, two way, two period crossover design.

56 Volunteers were enrolled.

I.1.1 Results

I.1.2 Results

Parameter	Arithm mean	DS	Arithm mean	DS	Geo Mean		Ratio T/R %	CI 90%
	TEST		REF		TEST	REF		
Cmax	406.59	224.58	392.72	231.93	350.13	327.19	107.01	.9892-1.1577
AUC_{0-t}	868.82	740.82	891.03	738.44	658.75	678.08	97.15	0.8822-1.0698
AUCinf	896.22	742.51	921.17	742.91	691.02	709.48	97.40	0.8848-1.0721

Clinical Efficacy
No new data.

Clinical Safety
No new data.

V OVERALL CONCLUSIONS

The applicant has demonstrated comparable bioavailability between test and reference products under fasted and fed conditions. Marketing authorisations may be granted for these products.

The company have given an understanding that they will update the SPC and patient leaflet in line with a possible future harmonisation referral of Omeprazole product information.

VI REVISION DATE

July 2011

VII UPDATES

This section reflects the significant changes following finalization of the initial procedure.

Scope	Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval / non approval
Transfer of ownership for PA 1284/11/1-3 to PA 749/2/1-3	National	PA Number and MAH details	17/09/2008	14/10/2008	Approval
Change in product name for PA 749/92/1-3 from 'Tulzol' to 'Omeprazole Teva Pharma'.	National	Product name	05/04/2011	23/06/2011	Approval