

IPAR



**Public Assessment Report for a
Medicinal Product for Human Use**

Scientific Discussion

Omeprazole Bluefish 40 mg gastro-resistant capsules
Omeprazole
PA1436/007/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. 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 HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

The Public Assessment Report (PAR) reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) 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 HPRA 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 HPRA 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 HPRA 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 authorisation 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 Bluefish 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

Tulzol 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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- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
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The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA's website at www.hpra.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 hepatic 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 issue 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 of a Certificate of Suitability (CEP).

The CEP also vouches for adequate stability of the active substance under defined conditions covering the period of time 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 other 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-carmin (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.

P.2. 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. As 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 that it is adequately manufactured. The test methods themselves have been assessed so that one can be confident that they will give reliable results.

Data from three manufacturing campaigns have been presented, which show that the process will produce the same product every time.

P.6 Packaging material

The packaging materials are bottles made of high density polyethylene (HDPE) and polypropylene (PP) caps with integral 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 guidelines requirements. This has shown that the capsules can be stored for up to 3 years under storage conditions, 'Do not store above 30°C. 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

C max

AUC_{0-t}

AUC_{0-INFINITY}

Point estimate %	90% Confidence Intervals	Coefficient of Variance %
81.80	71.65-93.39	34.18
91.46	83.72-99.92	22.47
91.82	84.03-100.32	22.50

Day 5 steady state fasting

C max

AUC_{ss}

Point estimate %	90% Confidence Intervals	Coefficient of Variance %
89.91	80.69-100.19	27.66
97.61	91.99-103.58	14.97

Single dose with high fat meal

C max

AUC_{0-t}

AUC_{0-INFINITY}

Point estimate %	90% Confidence Intervals	Coefficient of Variance %
102.57	80.70-130.36	66.03
87.11	75.32-100.74	36.53
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

C max

AUC_{0-t}

AUC_{0-INFINITY}

Point estimate %	90% Confidence Intervals	Coefficient of Variance %
120.30	109.08-132.67	24.17
98.65	92.99-104.64	14.43
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		
406.59	224.58	392.72	231.93	350.13	327.19	107.01	.9892-1.1577
868.82	740.82	891.03	738.44	658.75	678.08	97.15	0.8822-1.0698
896.22	742.51	921.17	742.91	691.02	709.48	97.40	0.8848-1.0721

Cmax

AUC_{0-t}

AUCinf

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.