

IPAR



PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules, Hard LANSOPRAZOLE
PA0749/135/001-002

The Public Assessment Report 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 approval of 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 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 IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules from Teva Pharma B.V. on 3rd December 2010 for the treatment of duodenal and gastric ulcer.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an ‘informed consent’ application. This means that the Marketing Authorisation Holder for Lansoprazole 15 mg and 30 mg Gastro-resistant Capsules (PA 1271/4/1-2), which are authorised medicinal products in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules. Therefore both have the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as one another and are manufactured the same way.

The original licensed application for which Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules by Teva Pharma B.V. is identical to, was licensed as an incoming mutual recognition procedure with Portugal as the reference member state (PT/H/113/01-02).

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA’s website at www.hpra.ie

Name of the product	Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules
Name(s) of the active substance(s) (INN)	Lansoprazole
Pharmacotherapeutic classification (ATC code)	A02BC03
Pharmaceutical form and strength(s)	Gastro-resistant capsules, hard 15 mg & 30 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA749/135/001-2
Marketing Authorisation Holder	Teva Pharma B.V.

II QUALITY ASPECTS

II.1. Introduction

This application is for Lansoprazole 15 mg and 30 mg Gastro-resistant Capsules.

II.2 Drug substance

The active substance is lansoprazole, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

II.3 Medicinal product

P.1 Composition

Each gastro-resistant capsule contains 15 mg or 30 mg of lansoprazole. The capsules also contain the following excipients: sugar spheres (containing sucrose and maize starch), sodium starch glycolate (type A), sodium laurilsulfate, povidone, potassium oleate, oleic acid, hypromellose, methacrylic acid- ethyl acrylate copolymer 1:1, triethylcitrate, titanium dioxide and talc. The capsule shell contains titanium dioxide (E171), hypromellose, carrageenan, potassium chloride and carnauba wax. The capsules have a white cap marked with the letter ‘L’ and a white body marked with

the numbers '15' or '30' depending on the product strength. The printing ink on the capsules contains shellac, propylene glycol, ammonium hydroxide, potassium hydroxide and black iron oxide (E 172).

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in the original licenced application in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specifications and the analytical methods used are identical to those described in the original licenced application.

P.6 Packaging material

The product is presented as aluminium blisters.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in the original licenced application in accordance with EU guidelines and demonstrates that the product is stable for 2 years when stored below 30°C.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Lansoprazole PA 1271/4/1-2 on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

Not applicable for this type of application.
No additional studies have been conducted which is acceptable.

III.3 Pharmacokinetics

Not applicable for this type of application.
No additional studies have been conducted which is acceptable.

III.4 Toxicology

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction or genotoxicity.
In two rat carcinogenicity studies, lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids associated with hypergastrinaemia due to inhibition of acid secretion.

Intestinal metaplasia was also observed, as were Leydig cell hyperplasia and benign Leydig cell tumours. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.

In mouse carcinogenicity studies dose-related gastric ECL cell hyperplasia developed as well as liver tumours and adenoma of rete testis.

The clinical relevance of these findings is unknown.

III.5 Ecotoxicity/environmental risk assessment

Not applicable for this type of application.

No additional studies have been conducted which is acceptable.

III.6 Discussion on the non-clinical aspects

Not applicable for this type of application.

No additional studies have been conducted which is acceptable as no additional non clinical issues are expected with this application.

IV CLINICAL ASPECTS

IV.1 Introduction

Lansoprazole is a well known active substance with established efficacy and tolerability.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Lanoprazole PA 1271/4/1-2 marketed by Bentley Pharmaceuticals Ireland Limited.

As this is an informed consent application this medicinal product is identical to the reference product lansoprazole PA 1271/4/1-2 which was licensed during a mutual recognition procedure with Portugal as the reference member state.

No additional clinical or safety studies are necessary and bioequivalence is assured as it contains the same quantitative and qualitative composition and is manufactured exactly the same as the reference product lansoprazole PA 1271/4/1-2.

The SPC and product information approved is in accordance with that accepted for the reference product Lanoprazole PA 1271/4/1-2 marketed by Laboratorios Davur S.L.U.

IV.2 Pharmacokinetics

Lansoprazole is a racemate of two active enantiomers that are biotransformed into the active form in the acidic environment of the parietal cells. As lansoprazole is rapidly inactivated by gastric acid, it is administered orally in enteric-coated form(s) for systemic absorption. Absorption and distribution

Lansoprazole exhibits high (80-90%) bioavailability with a single dose. Peak plasma levels occur within 1.5 to 2.0 hours. Intake of food slows the absorption rate of lansoprazole and reduces the bioavailability by about 50%. The plasma protein binding is 97%. Studies have shown that granules from opened capsules give equivalent AUC as the intact capsule if the granules are suspended in a small amount of orange juice, apple juice, or tomato juice mixed with a tablespoon of apple or pear puree or sprinkled on a tablespoon of yoghurt, pudding or cottage cheese.

Equivalent AUC has also been shown for granules suspended in apple juice administered through a naso-gastric tube.

Metabolism and elimination

Lansoprazole is extensively metabolised by the liver and the metabolites are excreted by both the renal and biliary route. The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19.

The enzyme CYP3A4 also contributes to the metabolism. The plasma elimination half-life ranges from 1 to 2 hours following single or multiple doses in healthy subjects.

There is no evidence of accumulation following multiple doses in healthy subjects. Sulphone, sulphide and 5-hydroxyl derivatives of lansoprazole have been identified in plasma. These metabolites have very little or no antisecretory activity.

A study with ¹⁴C labelled lansoprazole indicated that approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces.

Pharmacokinetics in elderly patients

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Peak plasma levels were not increased in the elderly.

Pharmacokinetics in paediatric patients

The evaluation of the pharmacokinetics in children aged 1 –17 years of age showed a similar exposure as compared to adults with doses of 15 mg for those below 30 kg of weight and 30 mg for those above. The investigation of a dose of 17 mg/m² body surface or 1 mg/kg body weight also resulted in comparable exposure of lansoprazole in children aged 2-3 months up to one year of age compared to adults.

Higher exposure to lansoprazole in comparison to adults has been seen in infants below the age of 2-3 months with doses of both 1.0 mg/kg and 0.5 mg/kg body weight given as a single dose.

Pharmacokinetics in hepatic insufficiency

The exposure of lansoprazole is doubled in patients with mild hepatic impairment and much more increased in patients with moderate and severe hepatic impairment.

CYP2C19 poor metabolisers CYP2C19 is subject to genetic polymorphism and 2-6 % of the population, called poor metabolisers (PMs), are homozygote for a mutant CYP2C19 allele and therefore lacks a functional CYP2C19 enzyme. The exposure of lansoprazole is several-fold higher in PMs than in extensive metabolisers (EMs).

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC03

Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H⁺/K⁺ ATPase of the parietal cells in the stomach. The inhibition is dose dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid.

Lansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphhydryl group of H⁺/K⁺ATPase causing inhibition of the enzyme activity.

Effect on gastric acid secretion:

Lansoprazole is a specific inhibitor of the parietal cell proton pump. A single oral dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by about 80%. After repeated daily administration for seven days, about 90% inhibition of gastric acid secretion is achieved.

It has a corresponding effect on the basal secretion of gastric acid. A single oral dose of 30 mg reduces basal secretion by about 70%, and the patients' symptoms are consequently relieved starting from the very first dose.

After eight days of repeated administration the reduction is about 85%. A rapid relief of symptoms is obtained by one capsule (30 mg) daily, and most patients with duodenal ulcer recover within 2 weeks, patients with gastric ulcer and reflux oesophagitis within 4 weeks.

By reducing gastric acidity, lansoprazole creates an environment in which appropriate antibiotics can be effective

against *H. pylori*.

IV.4 Clinical Efficacy

No clinical efficacy studies were conducted this is acceptable for this type of application as this is an informed consent application.

IV.5 Clinical Safety

No clinical safety studies were conducted this is acceptable for this type of application as this is an informed consent application.

Periodic Safety Update Reports (PSUR) submission should be submitted on a 3 yearly basis.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

As this is an informed consent application this medicinal product is identical to the reference product lansoprazole which was licensed during a mutual recognition procedure with Portugal as the reference member state.

No additional clinical or safety studies are necessary and bioequivalence is assured as it contains the same quantitative and qualitative composition and is manufactured exactly the same as the reference product lansoprazole.

V OVERALL CONCLUSIONS

Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules PA749/135/001-002 (MAH Teva Pharma B.V.) is the same as Lansoprazole PA 1271/4/1-2 marketed by Laboratorios Davur S.L.U.

Lansoprazole is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The HPRA, on the basis of the data submitted, considered that Lansoprazole 15 mg & 30 mg Gastro-resistant Capsules (PA749/135/001-2) was the same as the reference product and therefore granted a marketing authorisation.