

**LANSOPRAZOLE GASTRO-RESISTANT 15MG CAPSULES  
PL 17780/0251**

**LANSOPRAZOLE GASTRO-RESISTANT 30MG CAPSULES  
PL 17780/0252**

**UKPAR**

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PL 17780/0251**

**LANSOPRAZOLE GASTRO-RESISTANT 30MG CAPSULES  
PL 17780/0252**

**LAY SUMMARY**

The MHRA granted Winthrop Pharmaceuticals UK Limited Marketing Authorisations (licences) for the medicinal products Lansoprazole 15mg gastro-Resistant Capsules (PL 17780/0251) and Lansoprazole 30mg Gastro-Resistant Capsules (PL 17780/0252) on the 6<sup>th</sup> December 2005. These are prescription only medicines (POM) for the treatment of acid-related disorders of the upper gastro-intestinal tract, with the benefit of rapid symptom relief.

Lansoprazole Capsules contain the active ingredient lansoprazole, which acts by reducing gastric acidity, a key requirement for healing of acid-related disorders such as peptic ulcers.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Lansoprazole 15mg and 30mg Gastro-Resistant Capsules outweigh the risks, hence Marketing Authorisations have been granted.

**LANSOPRAZOLE GASTRO-RESISTANT 15MG CAPSULES  
PL 17780/0251**

**LANSOPRAZOLE GASTRO-RESISTANT 30MG CAPSULES  
PL 17780/0252**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Lansoprazole 15mg and 30mg Gastro-Resistant Capsules to Winthrop Pharmaceuticals UK Limited (PL 17780/0251-2) on 6<sup>th</sup> December 2005. The products are prescription only medicines.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to the original products Lanzor 15 and 30mg Capsules (Aventis, France).

The products contain the active ingredient lansoprazole and are indicated for the treatment of acid-related disorders of the upper gastro-intestinal tract, with the benefit of rapid symptom relief.

Lansoprazole is a proton pump inhibitor and inhibits gastric acid by blocking the hydrogen-potassium adenosine tri-phosphate enzyme system of the gastric parietal cell.

These applications for Lansoprazole 15mg Gastro-Resistant Capsules and Lansoprazole 30mg Gastro-Resistant Capsules were submitted at the same time and both depend on the bioequivalence study comparing the applicant's 30mg product with the Lanzor capsule of the same strength. Consequently, all sections of this Scientific Discussion refer to both products.

## PHARMACEUTICAL ASSESSMENT

### Active substance

INN:	Lansoprazole
Chemical Name:	2-[[[3-methyl-4-(2, 2, 2-trifluoroethoxy)- pyridine-2-yl]methyl]sulfinyl benzimidazole
Molecular Formula:	$C_{16}H_{14}F_3N_3O_2 \cdot S$
Molecular Weight:	369.37
Appearance:	White or beige solid

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance lansoprazole.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof of structure has been supplied for the active pharmaceutical ingredient.

All potential known impurities have been identified and characterised.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated and no indication of instability seen. The data support a retest period of 12 months when stored at 2-8°C in double PE bags placed in a metal drum with a metal clamp closure.

### Other ingredients

Other ingredients consist of hypromellose, talc, titanium dioxide, methacrylic acid-ethyl acrylate, triethyl citrate, sugar spheres, purified water and hard gelatin capsule (which itself consists of titanium dioxide E171, purified water, gelatin, and black printing ink). All excipients used in the capsule fill are routinely tested for compliance with their respective Ph Eur monograph. Hard gelatin capsules used comply with in-house specifications. The qualitative and quantitative composition of the printing ink is given and all ingredients comply with USP-NF requirements (iron oxide also meet EC quality requirements).

Satisfactory certificates of analysis have been provided for all ingredients.

Gelatin used in the manufacture of the capsules is the only material of animal or human origin used. Satisfactory certificates of suitability have been provided.

Both strength capsules are packaged in white HDPE bottles with tamper evident, screw cap closures containing silica gel as desiccant and a white tamper evident ring. Alternatively, the capsules are packaged in aluminium/aluminium blisters. Satisfactory specifications and certificates of analysis have been provided for the packaging components.

### **Product development and finished product**

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and reference products with satisfactory results. Comparative impurity studies have also been undertaken.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results at pilot-scale. Additionally, a commitment has been provided that the first full-scale commercial production batches will be validated.

The finished product specifications proposed for both release and shelf life are acceptable and provide an assurance of the quality and consistency of the finished product. The analytical methods used have been suitably validated. Batch analysis data has demonstrated compliance with the proposed release specification.

### **Stability of the product**

All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 18 months for the 15mg strength product packaged in the blister packs and 24 months for the 30 mg strength product packaged in the blister packs. They also support a shelf-life of 24 months (unopened) and 28 days (after opening) for product packaged in HDPE bottles with screw cap. Storage conditions are 'Do not store above 25°C. Store in the original package' for the blister packs and 'Do not store above 25°C. Keep the bottle tightly closed to protect from moisture' for the HDPE bottles.

### **Bioequivalence/bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches.

### **SPC, PIL, Labels**

The SPC, PIL and Labels are pharmaceutically acceptable.

## **CONCLUSION**

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.

## **PRECLINICAL ASSESSMENT**

These applications for generic products claim essential similarity to Lanzor 15 and 30mg Capsules (Aventis, France), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.



## CLINICAL ASSESSMENT

### 1. INTRODUCTION

These applications are submitted under Article 10.1(a)(iii) of the Directive 2001/83/EC. The applicant has claimed essential similarity to Lanzor 30mg capsules marketed in France by Aventis. The first Marketing Authorisation for lansoprazole hard capsules 30mg was in France in 1990 and subsequently in Germany in June 1993. In the UK it is marketed by Cyanamid of Great Britain (PL 00095/0302 and 0264), granted in the UK 23 February 1994 and 17 January 1996, respectively.

### 2. BACKGROUND

Lansoprazole is a member of a class of drugs called proton pump inhibitors. These drugs inhibit gastric acid by blocking the hydrogen-potassium adenosine tri-phosphatase enzyme system (the 'proton pump') of the gastric parietal cell. They are the treatment of choice for stricturing and erosive oesophagitis. The suspension formulation is especially useful to patients with difficulty in swallowing such as the elderly and those with advanced oesophageal strictures. In addition, proton pump inhibitors offer effective short-term therapy for gastric and duodenal ulcer; they are also used in combination with antibiotics for the eradication of *H. pylori*.

### 3. INDICATIONS

#### USES

Lansoprazole is effective in the treatment of acid-related disorders of the upper gastro-intestinal tract, with the benefit of rapid symptom relief.

#### INDICATIONS

- Healing and long-term management of Gastro Oesophageal Reflux Disease (GORD).
- Healing and maintenance therapy for patients with duodenal ulcer.
- Relief of reflux-like symptoms (eg. heartburn) and/or ulcer-like symptoms (eg. upper epigastric pain) associated with acid-related dyspepsia.
- Healing of benign gastric ulcer.
- Treatment and prophylaxis of NSAID-associated benign gastric ulcers, duodenal ulcers and relief of symptoms in patients requiring continued NSAID treatment.
- Long term management of pathological hypersecretory conditions including Zollinger-Ellison syndrome.
- Lansoprazole is also effective in patients with benign peptic lesions, including reflux oesophagitis, unresponsive to H<sub>2</sub> receptor antagonists.

#### Assessor's Comment

*These are consistent with those of the reference product licence.*

### 4. DOSE & DOSE SCHEDULE

*These are in line with those of the reference product licence*

### 5. TOXICOLOGY

This has been assessed separately. No new data are provided or needed. However, the applicant has submitted a Preclinical Expert summary.

## **6. CLINICAL PHARMACOLOGY**

### **6.1 Pharmacodynamics**

Lansoprazole acts by inhibiting, specifically, the Hydrogen/Potassium ATPase (proton pump) of the parietal cell in the stomach, the terminal step in acid production. This leads to the reduction of gastric acidity, a key requirement for healing of acid-related disorders such as peptic ulceration. A single dose of 30mg inhibits pentagastrin-stimulated acid secretion by approximately 80%, indicating effective acid inhibition from the first day of dosing.

### **6.2 Pharmacokinetics**

Peak plasma levels occur within 1.5 to 2 hours following oral administration of Lansoprazole. It has high bioavailability (80-90%). The plasma elimination half-life ranges from 1 to 2 hours after single or multiple doses in healthy subjects. Its plasma protein binding is high at 97%. Lansoprazole exhibits a prolonged pharmacological action providing effective acid suppression over 24 hours. Lansoprazole is metabolised substantially by the liver and is excreted by both the renal and biliary route.

### **6.3 Bioequivalence**

The applicant has submitted a two-part study to determine the bioequivalence between the applicant's Lansoprazole 30mg capsules and the reference product following a single and multiple oral dose administration under fasting conditions and after a multiple oral dose administration under fed conditions. Both single and multiple doses parts of the study were performed in 52 healthy male and female volunteers.

In each study period, the drug was administered once daily on seven consecutive days under fasting conditions: an eighth dose was administered on the eighth day morning, thirty minutes after the beginning of a high fat breakfast. Each period was separated by a washout of 14 days. Blood samples were obtained at frequent intervals up to 12 hours and 24 hours post dosing following single and multiple dosing respectively. Lansoprazole was analysed using HPLC.

Statistical analysis was performed using Parametric ANOVA on  $C_{max}$ ,  $T_{max}$ ,  $AUC_T$  (or  $AUC\tau$ ),  $AUC_{\infty}$ ,  $AUC_{T/\infty}$ , (or  $AUC\tau/\infty$ ),  $K_{el}$  and  $T_{1/2el}$ ; geometric confidence interval for  $C_{max}$ ,  $AUC_T$  (or  $AUC\tau$  and  $AUC_{\infty}$  based on In-transformed data;  $T_{max}$  rank transformed. Anova model was applied with regards to the following:

- Stratified by each of the three days (day 1, day 7, day 8)
- Fixed factors: treatment, period, sequence;
- Random factor: subject effect (nested within the sequence)

The criteria for bioequivalence were as follows:

- The 90% confidence interval for the exponential of the difference between the Test and the Reference product for the In-transformed parameter  $AUC_T$  and  $AUC_\infty$  should be between 80 and 125%
- The 90% confidence interval for the exponential of the difference between the Test and the Reference product for the In-transformed parameter  $C_{max}$  should be between 75 and 133.33%.

The results of the main pharmacokinetic parameters are summarised in the three tables presented below.

**Lansoprazole 30mg Capsule (N=52)**  
**Single dose: Fasting (Day 1)**

Parameter	Geometric LS Means		Ratio	90% Confidence Limits	
	TEST	REFERENCE		LOWER	UPPER
<b>C<sub>max</sub></b> (ng/ml)	905.9	927.2	97.71	88.69	107.63
<b>T<sub>max</sub></b> (hrs)	1.50	1.50			
<b>AUC<sub>t</sub></b> (ng.h/ml)	1914.4	2070.7	92.45	86.78	98.49
<b>AUC<sub>∞</sub></b> (ng.h/ml)	1987.2	2164.3	91.81	86.30	97.68

**Lansoprazole 30mg Capsule (N=52)**  
**Following Multiple dosing: Fasting (Day 7)**

Parameter	Geometric LS Means		Ratio	90% Confidence Limits	
	TEST	REFERENCE		LOWER	UPPER
<b>C<sub>max</sub></b> (ng/ml)	958.6	843.1	113.70	103.76	124.61
<b>T<sub>max</sub></b> (hrs)	1.50	1.75			
<b>AUC<sub>t</sub></b> (ng.h/ml)	2090.7	2033.7	102.80	97.02	108.92
<b>AUC<sub>∞</sub></b> (ng.h/ml)	2200.0	2165.0	101.62	96.84	106.62

**Lansoprazole 30mg Capsule (N=52)**  
**Following Multiple dosing: Fed (Day 8)**

Parameter	Geometric LS Means		Ratio	90% Confidence Limits	
	TEST	REFERENCE		LOWER	UPPER
<b>C<sub>max</sub></b> (ng/ml)	215.4	148.7	144.92	112.34	186.96
<b>T<sub>max</sub></b> (hrs)	4.50	3.33			
<b>AUC<sub>t</sub></b> (ng.h/ml)	757.4	479.8	157.87	124.80	199.71
<b>AUC<sub>∞</sub></b> (ng.h/ml)	1172.9	729.4	160.80	128.61	201.05

The Test formulation (Lansoprazole 30mg DR capsules) was shown to be bioequivalent to the Reference formulation only under fasting conditions following a single and multiple oral dose administration.

The essentially linear pharmacokinetics of Lansoprazole, particularly at this relatively low dose range, makes it likely that the lower-doses of Lansoprazole formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

Forty-eight (48) subjects experienced a total of one-hundred-fifty-one (151) adverse events during the study. Seventy-three adverse events (35 different types) were reported after the single dose administration of the Test product and seventy-eight adverse events (37 different types) were reported after the administration of the Reference product. No serious adverse events were reported.

#### **Assessor's Comment**

*The results of the fasted study indicate unequivocal equivalence. The 90% confidence intervals (CI) for the AUC and  $C_{max}$  ratios fall within the conventional 80-125% bioequivalence range in the fasting study, but outside this range in the fed one.*

*The outside conventional bioequivalence range of CI shown in the fed study can be accepted in the case of lansoprazole particularly with its high intra-subject variability; for this implies a large range of blood drug levels, even when the same product is administered to the same subject on different occasions.*

The study under the fed conditions shows a delay in absorption for both reference and test products. The fed study also shows both the reference and test products have their bioavailability reduced, although the reference product is more affected. However, this reduction is not clinically relevant and is consistent with literature data.

#### **7. EFFICACY**

No new data are required. The applicant has submitted copies of several publications with a summary review of the literature confirming the effectiveness of Lansoprazole capsules.

#### **8. SAFETY**

No new data are needed. However, the applicant has provided several copies of publications with a safety review from the literature. No new safety issues have been detected.

#### **9. EXPERT REPORT**

A satisfactory clinical expert report has been submitted with an appropriate CV.

#### **10. SUMMARY OF PRODUCT CHARACTERISTICS**

The text of the proposed summary of product characteristics is essentially the same as that of the reference product licence.

#### **11. PATIENT INFORMATION LEAFLET**

This is satisfactory.

#### **12. LABELLING**

These appear satisfactory.

**13. DISCUSSION**

Proton pump inhibitors, including Lansoprazole, have been available in the UK for many years. Their use is well established with recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted. When used as indicated, Lansoprazole has a favourable benefit-to-risk ratio. The hazard associated with Lansoprazole appears to be low and acceptable when considered in relation to its therapeutic benefits.

**14. CONCLUSION**

Overall, there are no clinical objections to the grant of a marketing authorisation for these applications. No new or unexpected safety concerns arise from these applications. The SPC, PIL and packaging are satisfactory and consistent with that for the reference product.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Lansoprazole 15 and 30mg Gastro-Resistant Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

### EFFICACY

Bioequivalence has been demonstrated between the applicant's Lansoprazole 30mg Capsules and Lanzor 30mg capsules (Aventis, France). Given that linear kinetics apply between the 15mg and 30mg capsules, that proportional formulae for the capsules have been used and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 15mg capsules is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Lanzor capsules

### RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with lansoprazole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**LANSOPRAZOLE GASTRO-RESISTANT 15MG CAPSULES  
PL 17780/0251**

**LANSOPRAZOLE GASTRO-RESISTANT 30MG CAPSULES  
PL 17780/0252**

**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation application on 14 <sup>th</sup> June 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 1 <sup>st</sup> July 2004
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 3 <sup>rd</sup> December 2004, and further information relating to the quality dossiers on 8 <sup>th</sup> June 2005.
4	The applicant responded to the MHRA's requests, providing further information on 29 <sup>th</sup> June 2005, and again on 28 <sup>th</sup> July 2005.
5	The application was determined on 6 <sup>th</sup> December 2005

**LANSOPRAZOLE GASTRO-RESISTANT 15MG CAPSULES  
PL 17780/0251**

**LANSOPRAZOLE GASTRO-RESISTANT 30MG CAPSULES  
PL 17780/0252**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
07/02/2006	Type IA variation	To change the blister packaging material from 'aluminium peelable ' to a 'printed aluminium foil for sealing'. The specifications and quality control method are the same for the current and proposed packaging (for 30mg capsules only).	Approved - 03/07/2006
05/06/2007	Leaflet update	User Testing report and leaflet	Approved - 04/10/2007
05/03/2009	Type II variation	To update the SmPC and the PIL in line with the brand leader, Zoton as per Article 30 of Directive 2001/83/EC	Approved - 08/04/2010
27/05/2009	Type IA variation	To register an increase in the shelf life of the finished product (as packaged for sale in Al/Al blisters) from 18 to 24 months, when stored at no more than 25 degrees Celsius in the authorised packaging material (for 15mg capsules only).	Approved - 24/06/2009
19/02/2010	Type IB variation	To increase the shelf life from 24 months to 36 months of Lansoprazole capsules when packaged in blisters. Section 6.3 (Shelf life) of the SmPC has been updated.	Approved - 04/03/2010
19/02/2010	Type IB variation	To change the storage condition of Lansoprazole capsules when packaged in blisters from 'Do not store above 25°C' to 'Do not store above 30°C'. Section 6.4 of	Approved - 04/03/2010



		the SPC (Special precautions for storage), PIL and label have been amended.	
29/10/2010	Type IB variation	To update Section 4.2 (Posology and administration) of the SPC following the outcome of the Article 46 Paediatric work-sharing procedure, DE/W/006/pdWS/001.	Approved - 05/11/2010
23/09/2011	Type IA variation	To register the other change(s) to the DDPS (section 3.3, 3.2.2, 3.4, 3.6.5) that does not impact on the operation of the pharmacovigilance system.	Approved - 20/10/2011
04/05/2012	Type IB variation	To update sections 4.4 (special warnings) and 4.8 (undesirable effects) of the SmPC in line with the agreed PhVWP and CMDh wording on the effects of proton pump inhibitors on magnesium blood levels in long terms users (CMDh/PhVWP/047/2012, dated March 2012) and on the increased risk of fractures of the hip, wrist and spine. As a consequence, the PIL has been updated.	Approved - 05/07/2012
20/11/2013	Type IA variation	To introduce a Summary of Pharmacovigilance System to replace the current DDPS.	Approved - 11/12/2013
16/12/2013	Type IB variation	To update sections 4.1, 4.2, 4.4 and 4.8 of the SPC in line with the reference product and QRD template. The change includes the addition of an indication which was previously patented for the reference product. As a consequence, the PIL has been updated.	Approved - 10/03/2014
13/12/2013	Type II variation	To update section 4.8 of the SPC to include the undesirable effect collagenous colitis, following a review of the PSURs 4 and 5 by the MHRA.	Approved - 10/03/2014

## **SUMMARY OF PRODUCT CHARACTERISTICS**

Following approval of variations on 10 March 2014 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.

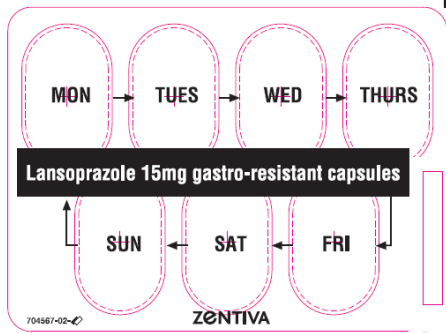
**PATIENT INFORMATION LEAFLET**

Following approval of a variation on 10 March 2014 the Patient Information Leaflet was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflets for products granted Marketing Authorisations at a national level are available on the MHRA website.

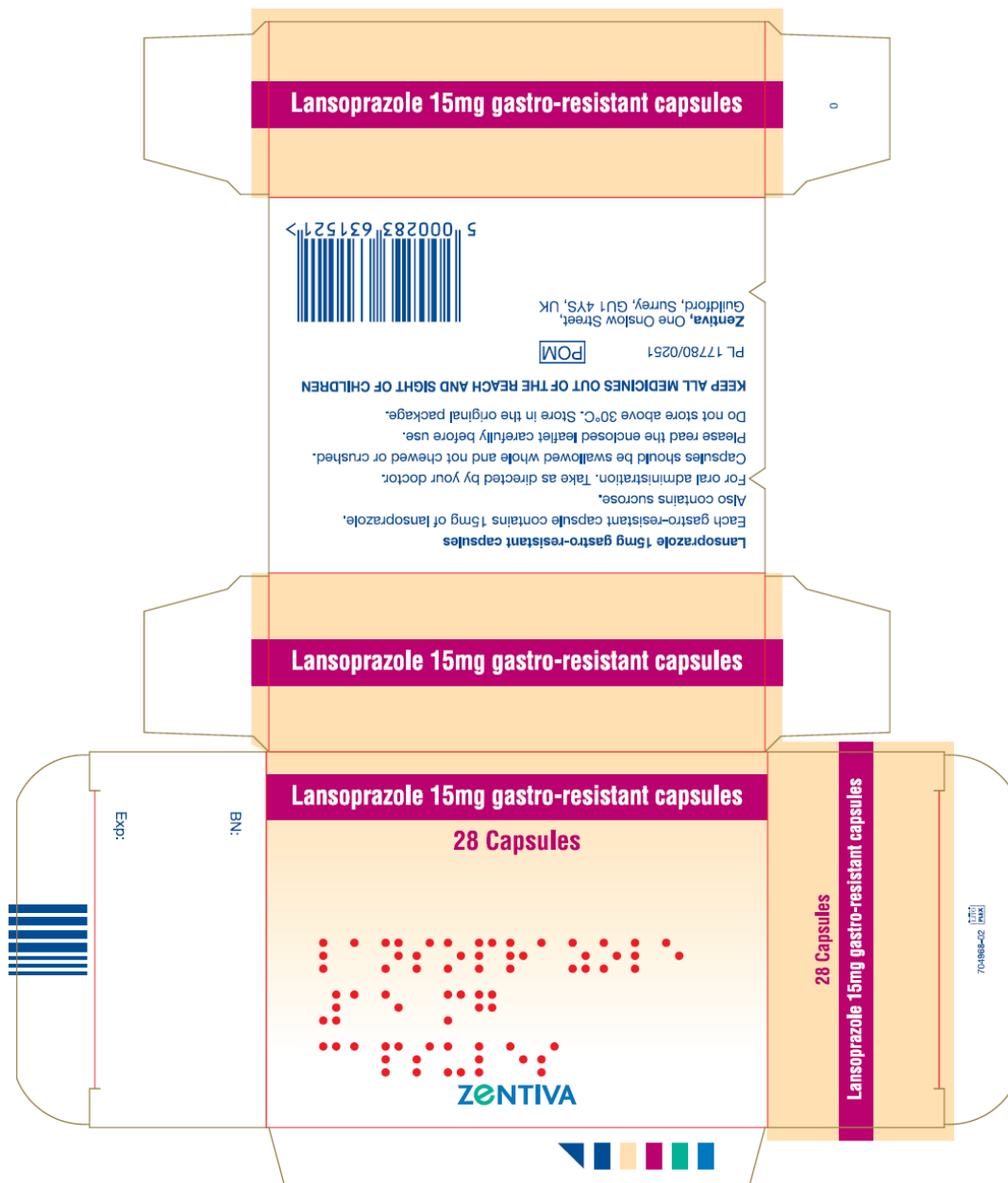
**LABELLING**

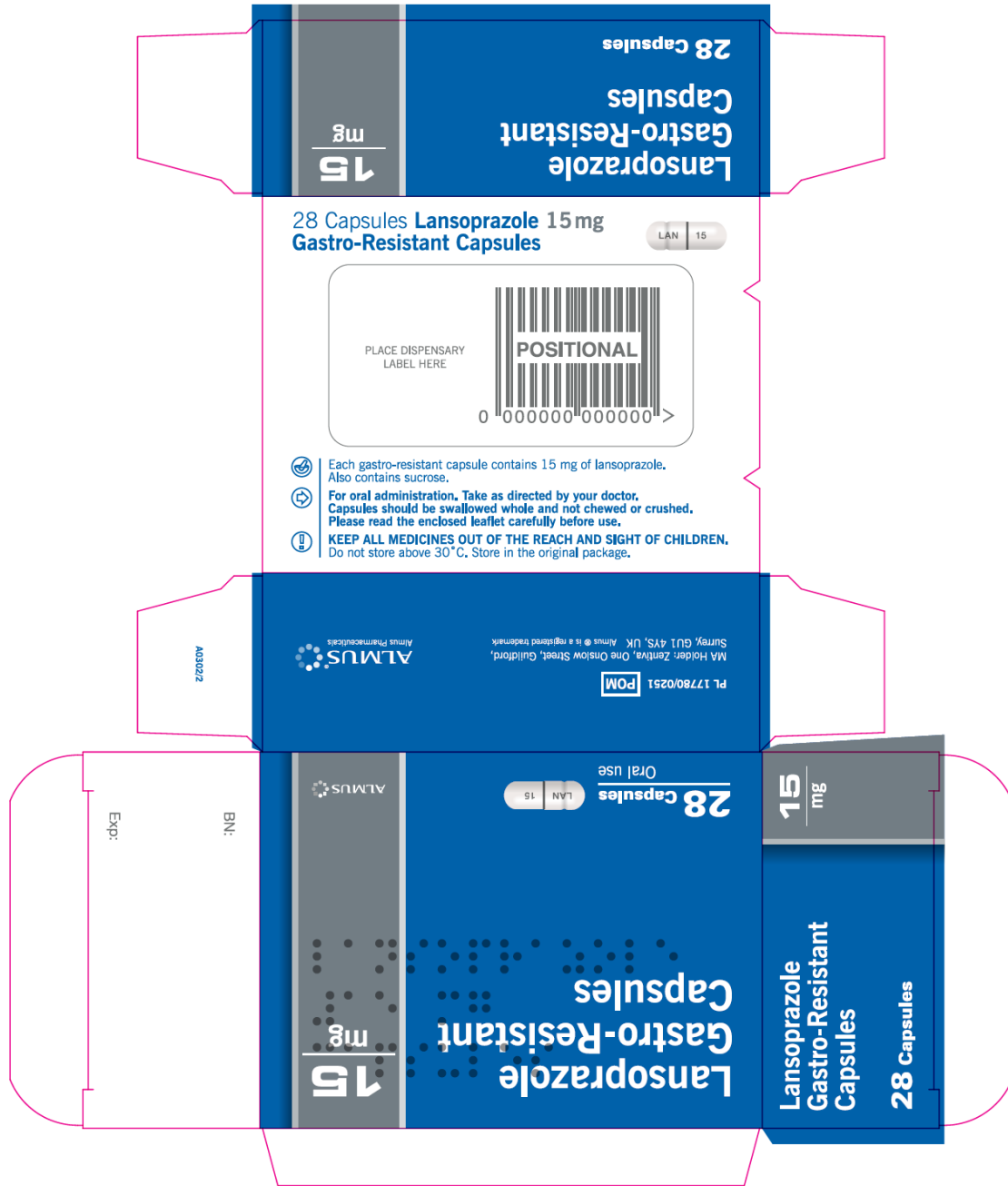
**Lansoprazole 15mg Capsules**

**Blister:**



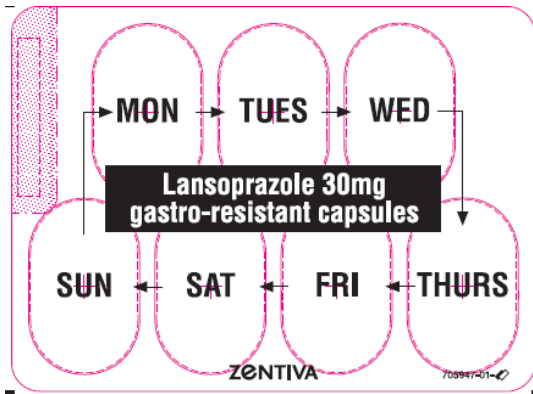
Cartons:





## Lansoprazole 30mg Capsules

**Blister:**









**ANNEX 1 – VARIATION ASSESSMENT REPORT**

<b>Type of Procedure:</b>	National
<b>Submission Type:</b>	Variation
<b>Submission Category:</b>	Type II
<b>Submission Complexity:</b>	Standard

**Reason:**

To update section 4.8 of the SmPC to include the undesirable effect collagenous colitis, following a review of Periodic Safety Update Reports (PSURs) 4 and 5 by the MHRA.

**Supporting Evidence**

Clinical overview

Reference to MHRA request arising from PSUR assessment

**Evaluation**

It was stated in the PSUR that, in view of the increasing cumulative data on collagenous colitis, the MAH should submit a type II variation with suitable supporting evidence to include this in the SmPC. The MAH has proposed this variation to comply with that request.

The MAH has submitted a Clinical Overview which includes suitable supporting information. Therefore, the addition of collagenous colitis with a frequency of 'not known' to Section 4.8 of the SmPC is approvable. The MAH has not submitted an updated leaflet because the term is already covered by Colitis which falls under the frequency 'very rare'. This is acceptable.

**Conclusion**

The variation may be approved.

**Decision - Approved**

Date: 10<sup>th</sup> March 2014