CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Esomeprazol Jubilant 20 mg and 40 mg, gastro-resistant tablets Jubilant Pharmaceuticals N.V., Belgium

esomeprazole (as magnesium)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2494/001-002/DC
Registration number in the Netherlands: RVG 111060, 111062

13 May 2013

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC05
Route of administration:	oral
Therapeutic indication:	see next page
Prescription status:	prescription only
Date of authorisation in NL:	12 March 2013
Concerned Member States:	Decentralised procedure with DE, DK, EE, LT, LV, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Esomeprazol Jubilant 20 mg and 40 mg, gastro-resistant tablets from Jubilant Pharmaceuticals N.V. The date of authorisation was on 12 March 2013 in the Netherlands.

The product is indicated for:

Adults
Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GERD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers

Patients requiring continued NSAID therapy
Healing of gastric ulcers associated with NSAID therapy.
Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.

Treatment of Zollinger Ellison Syndrome

Adolescents from the age of 12 years
Gastroesophageal Reflux Disease (GERD)
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GERD)

In combination with antibiotics in treatment of duodenal ulcer caused by Helicobacter pylori.

A comprehensive description of the indications and posology is given in the SPC.

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+K+-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nexium 20 mg and 40 mg, gastro-resistant tablets which has been registered in Sweden by AstraZeneca AB since 10 March 2000 (original product). In the Netherlands, Nexium 20 mg and 40 mg (NL License RVG 25387-25388) have been registered since 15 August 2000 by MRP SE/H/0211/001-002. In addition, reference is made to Nexium authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal

product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Nexium® 40 mg gastro-resistant tablets, registered in Denmark. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is esomeprazole magnesium (amorphous), an established active substance. The trihydrate form is described in the European Pharmacopoeia (Ph.Eur.*). Esomeprazole magnesium is an off-white to slightly coloured powder, which is slightly soluble in methanol and soluble in N,N-dimethyl formamide. Esomeprazole magnesium exhibits stereo isomerism and the S-isomer is manufactured. Esomeprazole magnesium exhibits polymorphism; the amorphous form is produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is manufactured in two processes. The active substance has been adequately characterized. Acceptable specifications have been adopted for the reagents and solvents.

Quality control of drug substance
The MAH has provided his own specification and also refers to the DMF specifications. In-house methods and specifications are described for the non-compendial tests. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided by the DMF-holder for three production-scale batches of both processes.

Stability of drug substance
Stability data on the active substance has been provided for 3 commercial-scale batches stored at 5°C (18 months/24 months) and 25°C/60% RH (6 months) of both processes. Out-of-specifications are seen at the

accelerated conditions. No changes or trends were seen at normal storage conditions. In view of the stability data, retest periods of 18 months for one process and 24 months for the other process at 2-8ºC are justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Esomeprazol Jubilant 20 mg is a light pink coloured, oblong, biconvex, coated tablet, debossed with 20 on one side and CE on the other.
Esomeprazol Jubilant 40 mg is a pink coloured, oblong, biconvex, coated tablet, debossed with 40 on one side and CE on the other.

The gastro-resistant tablets are packed in Aluminium/Aluminium blisters and polyethylene bottles with a tamper proof, polypropylene stock ribbed closure equipped with a desiccant canister.

The excipients are:
Sucrose
Maize starch
Hydroxypropylcellulose (E463)
Crospovidone (E1202)
Hydroxypropyl methylcellulose (E464)
Magnesium oxide
Talc (E553b)
Macrogol
Polysorbate 80 (E433)
Glycerol monostearate (E471)
Methacrylic acid ethyl acrylate copolymer dispersion 30 percent
Hypromellose phthalate
Microcrystalline cellulose (E460)
Ferric oxide red (E172)
Ferric oxide yellow (E172) (only for the 20 mg)
Povidone (E1201)
Pregelatinized starch
Colloidal hydrated silica
Titanium dioxide (E171)
Lactose monohydrate.

Except for the colour of the final Opadry film-coat, the 20 mg and 40 mg tablets are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were regarding the optimization of the composition and the performance of comparative dissolution studies with the innovator product. Bioequivalence studies have been performed comparing the 40 mg strength of drug product with the 40 mg reference product (Nexium) under fasted and fed conditions. The excipients used are well known and the choices of the packaging and manufacturing process are justified. The test batch used in the bioequivalence studies was manufactured according to the finalized manufacturing process and formula. The biowaiver of the 20 mg strength is justified on quality grounds. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process of the drug product consists of several stages. First the active substance is layered onto sugar spheres. The drug layered pellets from the previous stage are then coated with

different coating layers of which the last two coatings are the enteric coatings. The enteric coated pellets are then blended into a common blend which is compressed into tablets of either 20 or 40 mg strength. Finally the tablets are film-coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches of the common blend that was divided into three commercial scale batches of both tablet strengths.

Control of excipients
The excipients comply with Ph.Eur. or in-house standards. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, dissolution, uniformity of dosage units, assay, related substances, residual acetone, water content and microbial contamination. Except for water content and related substances the release and shelf-life limits are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three commercial-scale batches per strength stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (2 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in either HDPE bottles or Al-Al blisters. The stability data show an increase of impurities that is most pronounced at accelerated conditions and intermediate conditions. No other changes or trends were seen at the storage conditions. Photostability studies showed that the product is not sensitive to light. The proposed shelf-life of 24 months and storage condition 'Store below 25ºC in the original package and protect from moisture.' are justified. Additional in-use stability data are included for the polyethylene bottles and these fully support the claimed shelf-life. Addition of an in-use period in the SPC is deemed unnecessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose, monohydrate is prepared from milk and calf rennet. Milk is sourced from healthy animals in the same conditions as milk collected for human consumption (Complies with EU food hygiene regulations). The production of calf rennet complies with the requirements defined in regulation 999/2001 and other applicable EU legislation.

II.2 Non-clinical aspects

This product is a generic formulation of Nexium, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of esomeprazole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Esomeprazole is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Esomeprazol Jubilant 40 mg (Jubilant Pharmaceuticals N.V., Belgium) is compared with the pharmacokinetic profile of the reference product Nexiam 40 mg gastro-resistant tablets (AstraZeneca, Belgium) under fasted and fed conditions.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 21-42 years. Each subject received a single dose (40 mg) of one of the 2 esomeprazole formulations. The tablet was orally administered with 240 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected at pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20 and 24 hours after administration of the products.
The single dose, crossover study to assess bioequivalence is considered adequate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew for personal reasons. Pharmacokinetic and statistical analysis were carried out on 39 subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of esomeprazole under fasted conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4894 ± 2789	4940 ± 2808	1623 ± 622	3.0 (1.5 – 5.0)	1.4 ± 0.6
Reference	4867 ± 2590	4925 ± 2611	1824 ± 658	2.0 (1.0 – 4.0)	1.4 ± 0.5
***Ratio (90% CI)**	0.98 (0.92 – 1.05)	0.98 (0.92 – 1.05)	0.88 (0.81 – 0.95)	--	--
CV (%)	17.1	16.9	20.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of esomeprazole under fasted conditions, it can be concluded that

Esomeprazol Jubilant 40 mg and Nexiam 40 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II– fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 70 healthy male subjects, aged 19-42 years. Each subject received a single dose (40 mg) of one of the 2 esomeprazole formulations. The tablet was orally administered in solid form with 240 ml water within 30 min of serving a high-fat, high-caloric breakfast, containing 922.95 Kcal. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 14, 16 and 24 hours after administration of the products.

The single dose, crossover study to assess bioequivalence is considered adequate. The served breakfast consisted of at least 50% fat, which is the recommended meal for delayed formulations to evaluate the food interaction.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrew for personal reasons and one subject failed to follow up. These subjects were considered dropouts. Pharmacokinetic and statistical analysis were carried out on 68 subjects.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of esomeprazole under fed conditions.

Treatment N=68	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4798 ± 3203	4877 ± 3299	1332 ± 616	5.0 (2.5 – 6.5)	1.6 ± 0.8
Reference	4441 ± 3167	4498 ± 3209	1295 ± 571	5.0 (2.5 – 6.5)	1.5 ± 0.7
***Ratio (90% CI)**	1.13 (1.06 – 1.20)	1.13 (1.06 – 1.20)	1.03 (0.96 – 1.11)	--	--
CV (%)	21.3	21.1	26.0	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of esomeprazole under fed conditions, it can be concluded that Esomeprazol Jubilant 40 mg and Nexiam 40 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation to 20 mg strength
A biowaiver has been granted for the 20 mg strength, as the following criteria are fulfilled:
- The different strengths are manufactured by same manufacturing process.
- Esomeprazole Jubilant 20 mg tablets are developed as a dose proportional formula (scale down). The ratio between amounts of excipients is similar.
- The qualitative composition of Esomeprazol Jubilant tablets 20 mg and 40 mg is the same.
- Pharmacokinetics increase more than dose proportional. The highest dose is used in the bio-studies.
- The dissolution profile of Esomeprazol Jubilant tablets 40 mg is comparable to the 20 mg Esomeprazol Jubilant tablets, using dissolution testing at three pH values.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Esomeprazole was first approved in 2000 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of esomeprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Nexium.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. Safety issues specific to Esomeprazole Jubilant 20 mg & 40 mg gastro-resistant tablets were addressed using questions that used hypothetical situations to verify that the participant comprehended and was able to apply the information so as to make the correct decision.
Both rounds of testing showed that 100% of the participants were able to trace the information for the questions 100% of the time. Each of these participants showed they understood the information by answering the questions correctly 100% of the time. Based on the results, no revisions were made to the PIL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Esomeprazol Jubilant 20 mg and 40 mg, gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Nexium gastro-resistant tablets. Nexium is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Esomeprazol Jubilant 20 mg and 40 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 January 2013. Esomeprazol Jubilant 20 mg and 40 mg, gastro-resistant tablets were authorised in the Netherlands on 12 March 2013.

The date for the first renewal will be: 10 January 2018.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the on-going stability study at real time condition (25ºC ± 2ºC/60% RH ± 5% RH) of Esomeprazole 20 mg and 40 mg gastro-resistant tablets until the end of the proposed shelf life. Further, a commitment was made to place one commercial batch per year at real time condition (25ºC ± 2ºC/60% RH ± 5% RH).
- The MAH committed to evaluate the some of the set limits at the end of stability study.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached