Assessment report for pharmaceutical medicinal product

ESOMEPRAZOLE NORMON

2nd August 2017,
Division of Innovative Health Products and Services

Thai Food and Drug Administration

Name of product	Esomeprazole NORMON
Active Substance(s) (ATC code)	INN: Esomeprazole sodium (A02BC05)
Pharmaceutical form	Powder for solution for injection/infusion
Strength	Esomeprazole 40 mg
Route(s) of administration	Intravenous injection or intravenous infusion
Therapeutic indication(s)	**Indication as stated in SmPC:** Esomeprazole NORMON for injection and infusion is indicated for: Adults • Gastric antisecretory treatment when the oral route is not possible, such as: – Gastroesophageal reflux disease (GERD) in patients with esophagitis and/or severe symptoms of reflux. – Healing of gastric ulcers associate with NSAID therapy. – Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk. • Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers. Children and adolescents aged 1-18 years • Gastric antisecretory treatment when the oral route is not possible, such as: – Gastroesophageal reflux disease (GERD) in patients with erosive reflux esophagitis and/or severe symptoms of reflux. **Indications as stated in the patient information leaflet (PIL):** - ยานี้ใช้เพื่อยับยั้งการหลั่งกรดในกระเพาะอาหารเมื่อผู้ป่วยไม่สามารถกินยาได้ ได้แก่ - รักษาอาการกรดไหลย้อน ในผู้ป่วยหลอดอาหารอักเสบ และ/หรืออาการจากการไหลย้อนกลับของกรดขั้นรุนแรง - รักษาแผลในกระเพาะอาหารที่เกิดจากการใช้ยา ต้านการอักเสบที่ไม่ใช่สเตียรอยด์ - ป้องกันการเกิดแผลในกระเพาะอาหารและลำไส้เล็กส่วนต้นที่เกิดจากการใช้ยา

	ต้านการอักเสบที่ไม่ใช่สเตียรอยด์ในผู้ป่วยกลุ่มเสี่ยง - ป้องกันเลือดออกซ้ำของแผลในกระเพาะอาหารและลำไส้เล็กส่วนต้น หลังการห้ามเลือดโดยการส่องกล้อง
Submitted number and date of submission	1C 15114/60 (NG) 2 August 2017
E-Identifier Number	e5800010

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Assessment report for ESOMEPRAZOLE NORMON

Submitted number: 1C 15114/60 (NG)

E-identifier: E5800010 (sequence 0004)

(Manufacturing site: LABORATORIOS NORMON, S.A., Spain)

Submitted date: 2 August 2017

Part 1: Introduction and summary review

Gastro-esophageal reflux (GERD) is a condition where stomach acid persistently and regularly flows up into the esophagus. The acid in the esophagus causes heartburn and other symptoms, as well as possible tissue damage. Occasional acid reflux is quite common, often occurring as a result of overeating, lying down after eating, or eating particular foods. However, recurrent acid reflux, diagnosed as GERD, typically has other causes and risk factors and can have more serious complications. It occurs in people of all ages, and sometimes for unknown reasons. According to the ACG guideline[(1)] for diagnosis and management of gastroesophageal reflux disease 2013 suggested that Proton-pump inhibitors (PPIs) therapy is the therapy of choice for symptom relief and healing of erosive esophagitis (Strong recommendation, high level of evidence) and it is recommended for empirical therapy of GERD (Strong recommendation, moderate level of evidence).

Peptic ulcers are defects in the gastric or duodenal mucosa that extend through the muscularis mucosa. Under normal conditions, a physiologic balance exists between gastric acid secretion and gastroduodenal mucosal defense. Mucosal injury and, thus, peptic ulcer occur when the balance between the aggressive factors and the defensive mechanisms is disrupted. Aggressive factors, such as nonsteroidal anti-inflammatory drugs (NSAIDs), *H. pylori* infection, alcohol, bile salts, acid, and pepsin, can alter the mucosal defense by allowing back diffusion of hydrogen ions and subsequent epithelial cell injury. The defensive mechanisms include tight intercellular junctions, mucus, bicarbonate, mucosal blood flow, cellular restitution, and epithelial renewal.[(2)]

According to ACG practice guideline[(3)] on management of patients with ulcer bleeding, stated that in long-term prevention of recurrent bleeding ulcer daily PPIs is recommended in people with NSAID-associated bleeding ulcer who need for NSAIDs (strong recommendation for NSAIDs-associated) and in people with aspirin-associated bleeding ulcer who need for low-dose aspirin (Conditional recommendation)

Proton-pump inhibitors (PPIs) are the drugs of choice for the treatment of GERD. PPIs are substituted administered as enteric-coated tablets or capsules that pass through the stomach and are absorbed in the duodenum. They act on the proton pump molecule on the luminal surface of gastric parietal cells, resulting in inhibition of acid secretion. Esomeprazole was developed as the S-isomer of omeprazole as an improvement in its pharmacokinetic properties.[(4)]

Esomeprazole has been marketed in Thailand by several MAHs. The originator in Thailand is AstraZeneca, product name; Nexium®. The preparation is powder for solution for injection or infusion. There is solely strength available, 40 mg per vial. As well as generic availability in Thailand, there is only one MAH. Therefore, this product is an alternative for patients who cannot take the drug

by oral route. The review method is full review because this product do not has any assessment report from stringent regulatory agency.

Part 2: Summary of the dossier

2.1 Type of marketing authorization application

- **Product type:** Generic medicine (bioequivalence is not required)
- **Application type:** Generic medicinal product (bioequivalence is not required)
- **Review method:** Full review. The external expert review the Quality part

2.2 Administrative data

2.2.1 Product

Name of Product: Invented name	Esomeprazole NORMON
Active Substance(s)	Esomeprazole sodium
Strength	Esomeprazole 40 mg
Therapeutic class **(ATC Code)**	Proton pump inhibitors (A02BC05)
Pharmaceutical form	Powder for solution for injection/infusion
Route of administration	Intravenous injection or intravenous infusion
Drug Characteristics	White or almost white porous and uniform lyophilized powder
Packaging	vial, clear-colorless glass (type I)
Package size(s)	The vial stored in a box, each box contains 50 vials.

2.2.2 Source

- **Name and address of the applicant for importation**

  PACIFIC HEALTHCARE (THAILAND) CO. LTD, 1011 Supalai Grand Tower Room No. 01, 29th Floor, Rama 3 Rd, Chongnonsee, Yannawa, Bangkok 10120, Thailand

- **Name and address of the manufacturer(s) of the dosage form**

  Laboratorios Normon, S.A., No.6, Ronda de Valdecarrizo, 28760 Tres Cantos, Madrid, Spain

- **Name and address of the packaging and the secondary packaging**

  The same as stated in the name and address of the manufacturer

- **Name and address of the manufacturer(s) which take responsibility on inspection before release**

  The same as stated in the name and address of the manufacturer

- **Name and address of the manufacturer(s) of the active substance(s)**

  Union Quimico Farmaceutica S.A., Barcelona, Spain

Evaluation results
Laboratorios Normon, S.A., was licensed as manufacturer for modern medicine used in human. The manufacturer has been permitted both in sterile products and non-sterile products. The manufacturer has been certified GMP compliance by Ministerio De Sanidad, Servicios Sociales Eigualdad, Spain; membered of PIC/s. The manufacturer is also passed GMP clearance reviewed by Bureau of Drug Control.

Part 3: Analytical Physico-Chemical, Biological and Microbiological Documentation

3.1 Drug substance

3.1.1 General information

The drug substance is esomeprazole sodium, i.e. (S)-omeprazole sodium. It is the S-isomer of racemic omeprazole; the chiral center is at the sulphur atom. This drug substance is non-hygroscopic and freely soluble in water.

3.1.2 Manufacture

3.1.2.1 Manufacturer(s)

The Manufacturer is UNION QUIMICO FARMACEUTICA S.A. The manufacturing facilities are Factory No. 1 (Poligon Industrial El Pla, Av. Puigcerdà, No.9, C-17, Km.17.4, 08185 Llicà de Vall, Barcelona, Spain) performing step 1 and 2 and Factory No. 2 (Polígon Industrial Moli de les Planes, Font de Bocs S/N, C-35, Km. 57, 08470 Sant Celoni, Barcelona, Spain) performing step 3. The manufacturers got GMP certificate from Departament de Salut de la Generalitat de Catalunya which is equivalent to the WHO GMP**.**

3.1.2.2 Description of Manufacturing Process and Controls

For manufacturing process data, all steps have been described and explained in dossier.

Evaluation results

Manufacturing process and control of Drug substance is acceptable. Esomeprazole sodium was manufactured by Union Quimico Farmaceutica S**.**A**.**, Spain. The manufacturer has WHO GMP certified by Departament de Salut de la Generalitat de Catalunya, Spain.

3.1.3 Characterization

3.1.3.1 Elucidation of Structure and Other Characteristics

The manufacturer proposed synthetic route of Esomeprazole sodium and results of analysis such as elemental analysis, IR spectrum of working standard batch, H-NMR Spectrum, ^{13}C-NMR Spectrum, Mass Spectrum and all of physicochemical characterization in section 3.2.S.3.1 Elucidation of Structure and Other Characteristics.

3.1.3.2 Impurities

The known related substance impurities that may be found are (R)-Omeprazole sodium and Omeprazole impurities A-I according to European Pharmacopoeia.

All batches of the active pharmaceutical ingredient are tested for related substances by the in-house HPLC method in section *Analytical Procedures*.

3.1.4 Control of drug substance

3.1.4.1 Specifications

The drug substance specification including control of identity, purity, bioactivity and other general test has been provided.

3.1.4.2 Analytical procedures

The analytical procedures which comply with Ph. Eur. and USP are described.

3.1.4.3 Validation of Analytical Procedures

The company (Laboratorios Normon, S.A., Spain) provided the validation report of esomeprazole sodium .

The reports show that all of the results are comply with acceptable criteria**.**

3.1.4.4 Batch analysis

The results from COAs of Two batches shows the results are met all of the specification criteria described in "Test and specifications"

3.1.5 Reference materials

The data in reference materials from Laboratorios Normon (manufactured drug product) shows that Laboratorios Normon has prepared a secondary working standard of esomeprazole sodium (Union Quimico Farmaceutica S.A.) standardised with the primary working standard of omeprazole micronized (USP) for recheck the quality of drug substance follow the specification.

3.1.6 Container closure system

The container closure system for drug substance was stated in stability data. The packaging of drug substance is a double PE bag drum.

3.1.7 Stability

Stability studies are conducted on batches of Esomeprazole Sodium at degradation stability studies, accelerated storage condition tested at 0, 1, 2, 3 and 6 month and at long-term storage conditions tested every 6 months in the first year and then annually for 60 months. After stored in each condition, drug substance were tested appearance, identification, water and related substance

The degradation study was conducted by exposing the product to the stress conditions (temperature, humidity, neutral degradation, acid degradation, basic degradation, oxidation degradation and visible light).

From results we conclude that Esomeprazole Sodium is stable when stored in double polyethylene bag and drum (same characteristics as the industrial packaging) and should re-test every 3 year when store in a refrigerator (5ºC±3ºC)

Evaluation results
The manufacturer (Laboratorios Normon, S.A., Spain) described specification of esomeprazole sodium as drug substance complied with USP and Ph.Eur. The test confirmed the quality of esomeprazole sodium with validation method and COAs. The procedure evaluated by the expert suggested that the validation method is appropriate. Two batches analysis indicated the process validation is appropriate.

3.2 Drug product

3.2.1 Description and Composition of the drug product

The drug product comes in the form of white porous and uniform lyophilized powder. The 40 mg of esomeprazole is contained in 10 ml glass type I (in form of esomeprazole sodium)

Components	Quality Standard Reference		
Esomeprazole (sodium)	Current Eur. Ph. 9		
EDTA	Current Eur. Ph. 9		
Sodium hydroxide q.s.[2]	Current Eur. Ph. 9	-	
Water for injection q.s.[3]	Current Eur. Ph. 9		

The drug product vials and package leaflets are packed in cardboard boxes. The characteristic of the packaging material are adequately provided.

3.2.2 Manufacture

3.2.2.1 Manufacturer(s)

The manufacturer of the drug product is LABORATORIOS NORMON, S.A. Ronda de Valdecarrizo, 6 – 28760 Tres Cantos – Madrid (SPAIN). The GMP certificate issued by the competent authority of Spain.

3.2.2.2Description of manufacturing process and process control

The description of manufacturing process and process controls was satisfy provided. All operations are conducted following the good manufacturing practices (GMP) in a liquids-lyophilized injectable manufacturing zone.

The manufacturing process and in-process control was satisfy provided.

3.2.2.3 Controls of critical steps and intermediates

The critical steps together with limits and actions for critical in-process controls for esomeprazole finished product are provided.

3.2.2.4 Process validation and evaluation

. The standard protocol is attached in 3.2.P.3.5; Annex 1, including the results obtained from the different controls performed.

The finished product manufacturing process are adequately provided. The critical steps are controlled and have been validated. The in-process controls are adequate. Proven acceptable ranges (PARs) are considered to be adequately supported.

Laboratorios Normon, S.A., was licensed as manufacturer for modern medicine used in human. The manufacturer has been permitted both in sterile products and non-sterile products. The manufacturer has been certified GMP compliance by Ministerio De Sanidad, Servicios Sociales Eigualdad, Spain; membered of PIC/s. and GMP clearance certified by ThaiFDA.

3.2.3 Control of excipient

All of the specifications for excipients of this drug product are established by Ph.Eur. and analyzed in accordance with the analytical procedures described in its monograph of the Ph. Eur. current edition, none of excipient from human and animal.

3.2.4 Control of drug product

3.2.4.1 Specification

The drug product specification including control of identity and other general test has been provided.

3.2.4.2 Analytical procedure

The analytical procedures which comply with Ph. Eur. are described.

3.2.4.3 Validation of analytical procedure

All of the results from the validation study have been complied with their criteria.

3.2.4.4 Batch analyses

Two consecutive pilot batches analysis were provided and passed the specification.

3.2.4.5 Characterisation of Impurities

The impurities limitation was set by taking into account the results of the reference product. The details were adequately provided.

3.2.4.6 Justification of specification

The following tests have been analysed with the general techniques described in the current European Pharmacopoeia: pH, moisture content, clarity of the solution, colour of the solution, uniformity of dosage units, bacterial endotoxins, sterility and determination of particles.

For the specification of clarity of the solution, uniformity of dosage units, sterility and determination of particles have been complied with Ph. Eur.

The identification is proved by TLC and HPLC which are different chromatographic techniques and able to discriminate between compounds of closely related structure, according to ICH Q6A.

All other specifications in the drug product have been established according to the stability result studies. Also, the directive 2001/83/EC has been applied for the assay specification at release.

For the impurities specifications, they are similar to that reference drug, the limits for released and shelf-life has been established.

The air-tightness test is usually done at least one batch per year or each ten batches.

3.2.5 Reference standards or materials

The working standard of Esomeprazole sodium was provided The manufacturer performs the tests to ensure the quality of working standard by the test of description, identification (Sodium reaction (a) or IR identification (b)), humidity and assay (HPLC).

Evaluation results

The applicant provided the specification for control of excipient and drug product (released and shelf-life specification). Moreover, analytical procedure and the validation of analytical procedures are conducted. The results from batch analyses showed all batches complied with the specification.

For the drug product, the characterizations of the impurities are performed by HPLC. The specification of drug product almost followed Ph.Eur. In addition, the in-house specifications were justified and accepted.

The reference standard and material are from trustworthy providers and had been passed the specification before used.

This section is acceptable.

3.2.6 Container closure system

The primary packaging consists of type I glass vial, chlorobutyl rubber stopper and flip-off aluminium cap. The specification of 10-ml glass vial complied by European Pharmacopoeia current edition. The specification of vial glass was analyzed by Laboratorios Normon, S.A. The chlorobutyl rubber is provided by Laboratorios Normon, S.A and certified. The specification of chlorobutyl rubber was also analyzed by Laboratorios Normon, S.A. The flip-off aluminium cap is provided by Laboratorios Normon, S.A, and certified. The specification of flip-off aluminium cap was also analyzed by Laboratorios Normon, S.A.

3.2.7 Stability

The stability study was started to test the quality of the drug product under the following conditions; accelerated conditions, intermediate conditions, Long-term conditions, stability study of the reconstituted vials, and photosensitivity study in artificial light test (conducted according to ICH guideline Q1B).

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbiological contamination, the product should be used immediately.

Evaluation results

Drug product stability conforms to ASEAN Guideline. The 24 months shelf-life stored in the original container under storage conditions not above 30°C is acceptable. Storage exposed to normal indoor light outside the box is allowed not more than 24 hours. In-use stability (after reconstitution) shows that should be use immediately or keep in 30°C not more than 12 hours after reconstitution.

Assessor's conclusions on Quality

The quality data on manufacturing and quality control of drug substances and drug product is acceptable**.**

Part 4: Non-clinical documentation

N**/**A

Evaluation results
The information of non-clinical data is not required due to application type (generic product that does not require bioequivalence study).

Part 5: Clinical Study Reports

N**/**A

Evaluation results
The information of non-clinical data is not required due to application type (generic product that does not require bioequivalence study)

Part 6: Risk Management Plan

N/A

Evaluation results
This information of RMP is not required due to the reference product is classified in unconditional approval.

Label evaluation

Registered label from PACIFIC HEALTHCARE (THAILAND) CO. LTD is Unit carton label and inner label following Thai FDA 2009 ANNEX 3 Package insert and labeling rule.

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country's Registration Number	✓	✓
11	Name and address of Marketing Authorization Holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labeling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	n/a	n/a
15	Warning	✓	✓
16	Pack sizes	✓	✓

✓ Available or appropriate

n/a not available

INNER LABEL

No	Topic	Available	Appropiate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	X	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	X	✓
10	Country's Registration Number	X	✓
11	Name and address of Marketing Authorization Holder	X	✓
12	Name and address of manufacturer	✓	✓

✓ Available or appropriate

n/a not available

Patient information leaflet (PIL) evaluation

Patient information leaflet of Esomeprazole is adapted from SmPC and the originator SmPC. The information in Patient information leaflet is accurate, complete, and consistency with SmPC, quality data, non-clinical data and clinical data. The important information for patient is summarized in this PIL, however, user testing in Thais is required 12 months after receiving registered paper.

Summary of product characteristics (SmPC) evaluation

Summary of product characteristics conform to quality, non-clinical and clinical supporting data. The important information for healthcare professional is summarized in this SmPC conformed to SmPC of NEXIUM 40 mg powder for solution for injection/infusion approved in eMC.

Overall Benefit/risk assessment

Internal expert and external expert reviews the documents submitted to support the quality of Esomeprazole NORMON 40 mg, concluded that quality of Esomeprazole NORMON 40 mg is acceptable and pass the standard criteria.

The anti-secretory gastric acid efficacy of esomeprazole is well-established. In addition, Esomeprazole NORMON formulation was confirmed to be similar to reference drug NEXIUM®. The non-clinical and clinical studies can be refereed to the studies of the reference product. The internal reviewer concludes that the registered indication below is acceptable;

Esomeprazole NORMON for injection and infusion is indicated for:

Adults

• Gastric antisecretory treatment when the oral route is not possible, such as:

– Gastroesophageal reflux disease (GERD) in patients with esophagitis and/or severe symptoms of reflux.

– Healing of gastric ulcers associate with NSAID therapy.

– Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

• Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Children and adolescents aged 1-18 years

• Gastric antisecretory treatment when the oral route is not possible, such as:

– gastroesophageal reflux disease (GERD) in patients with erosive reflux oesophagitis and/or severe symptoms of reflux.

Therefore, the overall benefit/risk assessment supports approval of Esomeprazole NORMON, under the following condition

1) Submit the complete version of PIL after the user testing passes the criteria (user testing result should be submitted to Thai FDA within 12 months after the marketing authorization approval).

Internal reviewer

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(Kridiphol Janthranant, Pharm)

Evaluator

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(Worasuda Yoongthong, Ph.D.)

Reference

1. Philip O. Katz M, Lauren B. Gerson , MD, MSc and Marcelo F. Vela , MD, MSCR Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of GASTROENTEROLOGY. 2013;108(March 2013):308-28.
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3. Loren Laine MaDMJ, MD Management of Patients With Ulcer Bleeding. The American Journal of GASTROENTEROLOGY. 2012;107(March2012):345-60.
4. Björnsson EKaE. A review of esomeprazole in the treatment of gastroesophageal reflux disease (GERD). Therapeutics and Clinical Risk Management 2007;3(4):653-63.

Appendix 1

Appendix 2