CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

EMOXEN

Naproxen 500 mg + Esomeprazole 20 mg modified release tablets

ES/H/0863/001/DC

Date: 05/06/2024

This module reflects the scientific discussion for the approval of Emoxen 500 mg/20 mg modified release tablets. The procedure was finalised at 14/12/2023. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Emoxen 500 mg/20mg modified release tablets, from Bausch Health Ireland Ltd.
The product is indicated for the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, in patients who are at risk for developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric and/or duodenal ulcers and where treatment with lower doses of naproxen or of other NSAIDs is not considered sufficient.

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

This decentralised procedure concerns a generic application, which has been granted pursuant to Article 10.1 of Directive 2001/83/EC, claiming essential similarity with the innovator product Vimovo 500 mg/20 mg Modified Release Tablets (AstraZeneca AB) which has been registered in Sweden by *(*AstraZeneca AB, Sweden*)* since 02/02/2012 via decentralised procedure.

In this procedure the concerned member's states have been Czech Republic, Denmark, Finland, Hungary, Poland, Norway, Sweden, and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as modified release tablets containing 500 mg of naproxen and 20 mg of esomeprazole (as magnesium trihydrate) as active substances. The maximum daily dose is 1000 mg of naproxen and 40 mg of esomeprazole.

The product is available in HDPE bottles containing silica-gel desiccant with child resistant cap with an aluminium induction seal.

II.2 Drug Substance

[Naproxen]

The Applicant has used the CEP procedure.

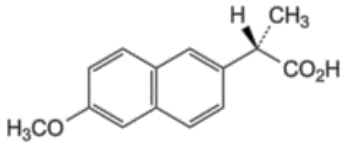
General Information

Nomenclature:

INN: Naproxen

Chemical name: (2S)-2-(6-Methoxynaphthalen-2-yl) propanoic acid
CAS-No: [22204-53-1]

Structure:



MW: 230.3
Molecular formula: $C_{14}H_{14}O_3$

General Properties:

It is a white or almost white, crystalline powder, practically insoluble in water, soluble in ethanol (96 per cent) and in methanol.

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM

[Esomeprazol magnesium trihydrate]

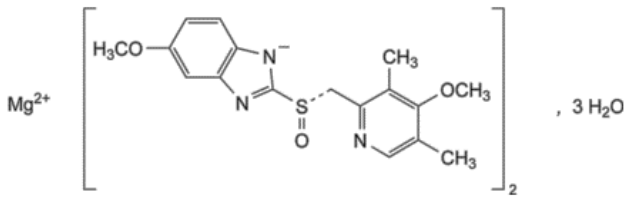
The Applicant has used the CEP procedure.

General Information

Nomenclature:

INN: Esomeprazol (*as magnesium trihydrate*)
Chemical name: Magnesium bis[5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethylpyridin-2-yl) methyl]sulfinyl]-1*H*-benzimidazol-1-ide] trihydrate
CAS-No: [217087-09-7]

Structure:



MW: 767.2
Molecular formula: $C_{34}H_{36}MgN_6O_6S_2,3H_2O$

General Properties:

White or slightly coloured powder, slightly hygroscopic, slightly soluble in water, soluble in methanol, practically insoluble in heptane.

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

II.3 Medicinal Product

Drug Product

Description of the product

The dosage form consist of yellow, oblong of 19.4 mm length, biconvex, plain on both sides tablets and is packaged in HDPE bottles.
Each tablet contains as active substances 500 mg of naproxen and 20 mg of esomeprazole (as magnesium trihydrate). The other ingredients (excipients) are: in tablet core colloidal silica anhydrous, methacrylic acid - ethyl acrylate copolymer (1:1), sodium laurilsulfate, polysorbate 80, glycerol monostearate 40-55, triethyl citrate, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, microcrystalline cellulose, magnesium oxide, light, povidone, calcium stearate; in the coating: hypromellose (E464), macrogol (E1521), titanium dioxide (E171), iron oxide yellow (E172).

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well defined.
Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin except lactose monohydrate and for it, suitable information is presented to guarantee compliance with the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents*.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in HDPE bottles containing silica-gel desiccant with child resistant cap with an aluminium induction seal. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf life and storage conditions are properly established.

Shelf life: 2 years

Storage conditions: This medicinal product does not require any special temperature storage conditions.
Store in the original package and keep the bottle tightly closed in order to protect from moisture.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Emoxen 500 mg/ 20 mg modified release tablets is a FDC including compounds for which there is sufficiently documented human experience of their individual and combined use. Therefore, safety studies in animals are not required.

Pharmacodynamic, pharmacokinetic and toxicological properties of naproxen and esomeprazole are well known. As both naproxen and esomeprazole are widely used, well-known active substances, the Applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Emoxen 500 mg/ 20 mg modified release tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Naproxen + Esomeprazole is a well-known FDC with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of a modified release formulation, the MAH has submitted two bioequivalence studies with the 500 mg/20 mg strength according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms, which are discussed below.

IV.2 Pharmacokinetics

Biowaiver

NA. Only one strength has been applied.

Bioequivalence studies

1. Study code ARL/21/266

The studies were conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical site: Accutest Research Lab (I) Pvt. Ltd. A-31, MIDC, T.T.C. Industrial Area, Khairane, Navi Mumbai – 400 709, Maharashtra, India.

Analytical centre: Accutest Research Lab (I) Pvt. Ltd. A-31, MIDC, T.T.C. Industrial Area, Khairane, Navi Mumbai – 400 709, Maharashtra, India.

A randomised, single-dose, two-treatment, four-period, two sequence, crossover replicate bioequivalence study was carried out under fasted conditions in 52 healthy subjects (6 female and 46 male), aged 20 - 44 years. Each subject received a single dose 500 mg/20 mg tablet) of one of the two FDC formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of 10 days between period II and period III and 08 days between period III and period IV.

The design of the studies is acceptable.

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.

The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Table 1. Pharmacokinetic parameters of naproxen (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} mcg/ml*h	$AUC_{0-\infty}$ mcg/ml*h	C_{max} mcg/ml	t_{max} h
Test	1457.68±229.25	1548.66± 270.42	71.42 ± 12.80	4.50 (1.0– 24.0)
Reference	1367.33± 317.32	1454.03± 356.15	68.64 ± 18.69	5.00 (2.50–24.0)
***Ratio (90% CI)**	111.31 (103.91 – 119.24)		108.72 (101.25 – 116.74)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration.at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
tmax Time until Cmax is reached

*ln-transformed values

Table 2. Pharmacokinetic parameters of esomeprazole (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	AUC_{0-t} ng/ml*h	$AUC_{0-\infty}$ ng/ml*h	C_{max} ng/ml	t_{max} h
Test	3053.27± 2370.67	3172.48±2574.4	997.55 ± 527.28	0.83 (0.33– 2.5)
Reference	2791.65±2037.7	2894.66±2192.4	991.28± 590.56	0.67 (0.33– 2.03)
***Ratio (90% CI)**	109.69 (103.68 – 116.06)	NA	104.10 (96.14 – 112.72)	

C_{max} Maximum plasma concentration
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration.at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
tmax Time until Cmax is reached

*ln-transformed values

2. Study code ARL/21/267

Clinical site: Accutest Research Lab (I) Pvt. Ltd. A-31, MIDC, T.T.C. Industrial Area, Khairane, Navi Mumbai – 400 709, Maharashtra, India.

Analytical centre: Accutest Research Lab (I) Pvt. Ltd. A-31, MIDC, T.T.C. Industrial Area, Khairane, Navi Mumbai – 400 709, Maharashtra, India.

A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy subjects (4 female and 32 male), aged 18 - 44 years. Each subject received a single dose 500 mg/20 mg tablet) of one of the two FDC formulations. The tablet was orally administered with 240 ml water and a high fat, high-calories breakfast that was started by subjects 30 minutes prior to drug administration, after an overnight fast of at least ten hours. There were two periods, separated by a washout period of 13 days.

The design of the studies is acceptable.

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Table 1. Pharmacokinetic parameters of naproxen (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** **mcg/ml*h**	**$AUC_{0-\infty}$** **mcg/ml*h**	**C_{max}** **mcg/ml**	**t_{max}** **h**
Test	1465.39± 265.38	1571.40± 313.69	64.08 ± 11.17	13.50(3.0–24.03)
Reference	1387.35± 293.07	1527.04± 366.26	68.26 ± 15.75	16.00(3.0–36.0)
***Ratio (90% CI)**	106.15 (101.55 - 110.95)		95.28 (88.77 - 102.27)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration.at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
tmax Time until Cmax is reached

*ln-transformed values

Table 2. Pharmacokinetic parameters of esomeprazole (non-transformed values; arithmetic mean ± SD, tmax median, range)

Treatment	**AUC_{0-t}** **ng/ml*h**	**$AUC_{0-\infty}$** **ng/ml*h**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	2700.90± 983.86	2747.24±1011.8	750.13± 192.53	2.33 (1.0 – 4.5)
Reference	2465.42± 870.12	2518.61± 898.22	725.73± 169.17	2.0 (1.00– 5.00)
***Ratio (90% CI)**	108.75 (101.33 - 116.71)		103.18 (95.59 - 111.37)	

C_{max} Maximum plasma concentration **AUC_{0-t}** Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration.at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t} **tmax** Time until Cmax is reached

*ln-transformed values

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies EMOXEN 500 mg/ 20 mg modified release tablets is considered bioequivalent with Vimovo 500 mg/ 20 mg modified-release tablets.

IV.3 Pharmacodynamics

NA

IV.4 Clinical efficacy

NA

IV.5 Clinical safety

NA

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to EMOXEN 500 mg/ 20 mg modified release tablets.

IV.7 Discussion on the clinical aspects

Based on the submitted bioequivalence studies EMOXEN 500 mg/ 20 mg modified release tablets is considered bioequivalent with Vimovo 500 mg/ 20 mg modified-release tablets, as explained in section IV.2.

V. USER CONSULTATION

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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Emoxen 500 mg/ 20 mg modified release tablets is found adequate. There are no objections to the approval of Emoxen 500 mg/ 20 mg modified release tablets from a non-clinical and clinical point of view. Bioequivalence between the test and

reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.