IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Naproxen / Esomeprazole Rowex Ltd 500 mg/20 mg modified-release tablets
Naproxen
Esomeprazole magnesium trihydrate
PA0711/325/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Naproxen / Esomeprazole Rowex Ltd 500 mg/20 mg Modified-release tablet, from Rowex Ltd. on 15th November 2024 for the symptomatic treatment in adults 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.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a generic application.

The HPRA was RMS in the decentralised procedure and the CMS was AT.

Naproxen/Esomeprazole Rowex 500 mg/20 mg Modified-release Tablet is a prescription only medicine.

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

Name of the product	Naproxen / Esomeprazole Rowex Ltd Modified-release tablet
Name(s) of the active substance(s) (INN)	Naproxen, esomeprazole magnesium trihydrate
Pharmacotherapeutic classification (ATC code)	M01AE52
Pharmaceutical form and strength(s)	500 mg/20 mg, Modified-release tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0711/325/001
Marketing Authorisation Holder	Rowex Ltd.
MRP/DCP No.	IE/H/1255/001/DC
Reference Member State	IE
Concerned Member State	AT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Naproxen/Esomeprazole Rowex Ltd. 500 mg/20 mg Modified-release tablet.

II.2 Drug substance

The active substances are naproxen and esomeprazole magnesium trihydrate, both are established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications are considered adequate to control the quality and meets current pharmacopeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each modified-release tablet contains 500 mg naproxen and 20 mg esomeprazole (as magnesium trihydrate).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

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

P.3 Manufacture of the Product

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

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

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

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

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Naproxen/Esomeprazole Rowex Ltd 500 mg/20 mg Modified-release tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

These active substances are generic formulations of Vimovo 500 mg/20 mg Modified-release tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of naproxen and esomeprazole magnesium trihydrate are well known.

III.2 Ecotoxicity/environmental risk assessment

Since Naproxen/Esomeprazole Rowex 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.

III.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of naproxen and esomeprazole magnesium trihydrate are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As naproxen and esomeprazole magnesium trihydrate are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Naproxen and esomeprazole are well known active substances with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Vimovo 500 mg/20 mg Modified-release tablets by Grunenthal GmbH authorised in Ireland since 21/12/2010 in procedure NL/H/1848/001/DC.

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Naproxen/Esomeprazole Rowex is compared with the pharmacokinetic profile of the reference product Vimovo 500 mg/20 mg Modified-release tablet.

Study 1
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out in healthy adult human subjects under fasting conditions. Naproxen/Esomeprazole Rowex was compared to the reference product Vimovo 500 mg/20 mg modified-release tablets.

Study 2
A randomised, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Naproxen/Esomeprazole Rowex, with Vimovo 500 mg/20mg Modified-release tablet was carried out in healthy adult human subjects under few conditions.

In both studies, based on the pharmacokinetic parameters of the active substances, the reference tablet Vimovo 500 mg/20 mg Modified-release tablet and test tablet Naproxen/Esomeprazole Rowex are bioequivalent with regards to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Vimovo 500 mg/20 mg Modified-release tablet marketed by Grunenthal GmbH.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

<u>Absorption</u>
Naproxen
After single dose application the time to peak plasma concentration is achieved after 3 to 5 hours, however, food intake results in further delay up to 8 hours or more. At steady state following administration of Naproxen/Esomeprazole Rowex twice daily, peak plasma concentrations of naproxen are reached within a median time of 3 hours following both the morning and the evening dose.

Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an *in vivo* bioavailability of 95%.

Steady-state levels of naproxen are reached in 4 to 5 days.

Esomeprazole
Following administration of Naproxen/Esomeprazole Rowex twice daily, esomeprazole is rapidly absorbed with peak plasma concentration reached within a median time of 0.5-0.75 hours following the morning and evening dose on both the first day of administration and at steady state. After repeated bid dosing of Naproxen/Esomeprazole Rowex, the Cmax was 2-3 times

higher, and the AUC 4-5 times higher, as compared to the first day of dosing. This is probably partly a result of an increased absorption due to the pharmacodynamic effect of esomeprazole with increased intragastric pH, leading to reduced acid degradation of esomeprazole in the stomach. A decrease of first pass metabolism and systemic clearance of esomeprazole with repeated dosing also contributes to the higher plasma concentrations at steady state (see Linearity/non-linearity).

Concomitant administration with food
Administration of Naproxen/Esomeprazole Rowex together with food does not affect the extent of absorption of naproxen but significantly delays the absorption by about 8 hours and decreases peak plasma concentration by about 12%.

Administration of Naproxen/Esomeprazole Rowex together with food does not delay the absorption of esomeprazole but significantly reduces the extent of absorption, resulting in 52% and 75% reductions of area under the plasma concentration versus time curve and peak plasma concentration, respectively.

Administration of Naproxen/Esomeprazole Rowex 30 minutes before food intake has only minimal or no effect on the extent and time to absorption of naproxen and has no significant effect on the rate or extent of esomeprazole absorption compared to administration under fasted conditions.

Distribution
Naproxen
Naproxen has a volume of distribution of 0.16 l/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma.

Esomeprazole
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Biotransformation
Naproxen
30% of naproxen is metabolized in the liver by the cytochrome P450 system (CYP), primarily CYP2C9, to 6–0–desmethyl naproxen. Neither the parent drug nor the metabolites induce metabolizing enzymes. Both naproxen and 6–0–desmethyl naproxen are further metabolised to their respective acylglucuronide conjugated metabolites.

Esomeprazole
Esomeprazole is completely metabolised by the CYP system. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma. The major metabolites of esomeprazole have no effect on gastric acid secretion.

Elimination
Naproxen
Following administration of Naproxen/Esomeprazole Rowex twice daily, the mean elimination half-life for naproxen is approximately 9 hours and 15 hours following the morning and evening dose, respectively, with no change with repeated dosing.

The clearance of naproxen is 0.13 ml/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (< 1%), 6-0-desmethyl naproxen (< 1%) or their conjugates (66% to 92%). Small amounts, 3% or less of the administered dose, are excreted in the faeces. In patients with renal failure metabolites may accumulate.

Esomeprazole
Following administration of Naproxen/Esomeprazole Rowex twice daily, the mean elimination half-life for esomeprazole is approximately 1 hour following both the morning and evening dose on day 1, with a slightly longer elimination half-life at steady state (1.2-1.5 hours).

Total plasma clearance of esomeprazole is about 17 l/h after a single dose and about 9 l/h after repeated administration.

Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

Linearity/non-linearity

Naproxen

At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses.

Esomeprazole

The area under the plasma esomeprazole concentration-time curve increases with repeated administration of Naproxen/Esomeprazole Rowex. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is partly due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. An increased absorption of esomeprazole with repeated administration of Naproxen/Esomeprazole Rowex probably also contributes to the time-and dose-dependency (see Absorption).

Special populations

Renal impairment

The pharmacokinetics of Naproxen/Esomeprazole Rowex has not been determined in patients with renal impairment.

Naproxen: Naproxen pharmacokinetics has not been determined in subjects with renal impairment.

Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen/Esomeprazole Rowex is contraindicated for use in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Esomeprazole: No studies have been performed with esomeprazole in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Hepatic impairment

The pharmacokinetics of Naproxen/Esomeprazole Rowex has not been determined in patients with impaired hepatic function.

Naproxen: The pharmacokinetics of naproxen has not been determined in subjects with hepatic impairment.

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for the naproxen component of Naproxen/Esomeprazole Rowex dosing is unknown but it is prudent to use the lowest effective dose.

Esomeprazole: The metabolism of esomeprazole in patients with mild to moderate hepatic impairment may be impaired. The metabolic rate is decreased in patients with severe hepatic impairment resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole.

Patients with severe hepatic insufficiency should not receive Naproxen/Esomeprazole Rowex.

Elderly

There is no specific data on the pharmacokinetics of Naproxen/Esomeprazole Rowex in patients over age 65.

Naproxen: Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in older people, however the unbound fraction is < 1% of the total naproxen concentration. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some older patients.

Esomeprazole: The metabolism of esomeprazole is not significantly changed in older subjects (71-80 years of age).

Poor CYP2C19 metabolisers

Esomeprazole: Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were about 60% higher.

These findings have no implications for the posology of Naproxen/Esomeprazole Rowex.

Gender
Esomeprazole: Following a single dose of 40 mg esomeprazole the mean area under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of Naproxen/Esomeprazole Rowex.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: naproxen and esomeprazole ATC code: M01AE52
Mechanism of action
Naproxen/Esomeprazole Rowex has been developed as a sequential-delivery tablet formulation combining an immediate release esomeprazole magnesium layer and an enteric coated delayed-release naproxen core. As a result, esomeprazole is released in the stomach prior to the dissolution of naproxen in the small intestine. The enteric coating prevents naproxen release at pH levels below 5 providing protection against possible local gastric toxicity of naproxen.

Due to the delayed-release of naproxen, Naproxen/Esomeprazole Rowex is not intended for, and has not been studied in, acute pain.

Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Esomeprazole is the *S*-enantiomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. 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.

IV.4 Clinical Efficacy

The efficacy of Naproxen/Esomeprazole Rowex in the proposed indications is established in clinical use. No new clinical efficacy studies are provided, and none are required.

IV.5 Clinical Safety

The overall safety profile of Naproxen/Esomeprazole Rowex is established and generally known. No new safety studies are provided, and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference medicinal product.

Risk Management Plan
A Risk Management Plan, version 1.0, dated 21 September 2022 has been submitted, 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 Naproxen + Esomeprazole magnesium 500mg + 20 mg. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

Naproxen and esomeprazole are well-known active substances that have been widely marketed.

Naproxen/Esomeprazole Rowex is a generic form of Vimovo 500 mg/20 mg Modified-release tablets from Grunenthal GmbH, which is a well-known medicinal product approved in Europe 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.

Naproxen/Esomeprazole Rowex is a prescription-only medicinal product in Ireland.

The content of the SmPC approved during this decentralised procedure is closely aligned with the reference product Vimovo 500 mg/20 mg modified-release tablets from Grunenthal GmbH.

V. OVERALL CONCLUSIONS

Naproxen/Esomeprazole Rowex 500 mg/20 mg Modified-release tablet is a generic form of Vimovo 500 mg/20 mg Modified-release tablets from Grunenthal GmbH. Vimovo is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considered that Naproxen/Esomeprazole Rowex 500 mg/20 mg Modified-release tablet demonstrated bioequivalence with the reference medicinal product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

19.09.2029