CBG MEB

Public Assessment Report

Scientific discussion

Naproxen Aurobindo 250 mg and 500 mg, tablets

(naproxen)

NL/H/3472/001-002/MR

Date: 1 November 2016

This module reflects the scientific discussion for the approval of Naproxen Aurobindo 250 mg and 500 mg, tablets. The procedure was finalised on 11 April 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Naproxen Aurobindo 250 mg and 500 mg, tablets from Aurobindo Pharma B.V.

The product is indicated for:

Adults:
Treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, acute gout, acute musculo skeletal disorders and dysmenorrhoea.

Children:
Juvenile rheumatoid arthritis

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the reference product Naprosyn which has been registered in the United Kingdom by Roche Products Limited since 9 February 2009. The innovator product which has been authorised in the EEA for not less than 10 years is Naprosyn 250 mg tablets, first registered in Portugal by Roche Farmacêutica Quimica, Lda in 1973.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Spain, Finland, Luxembourg, Norway, Poland, Portugal, Romania, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Naproxen Aurobindo is a tablet in two strengths:
250 mg tablets - yellow coloured, mottled, biconvex, bevelled edged, round shape, uncoated tablets debossed with ‘T’ & ‘18’ on either side of break line on one side and other side plain
500 mg tablets - yellow coloured, mottled, biconvex, capsule shape, uncoated tablets debossed with ‘T’ & ‘20’ on either side of break line on one side and other side plain

Each tablet contains 250 mg or 500 mg naproxen.

The tablets are packed in clear PVC/PE/PVdC-aluminium foil blister packs and white opaque HDPE-containers closed with white opaque polypropylene stock ribbed closure with wad having induction sealing liner.

The excipients are lactose monohydrate, maize starch, sodium starch glycolate, povidone (E1201), yellow iron oxide (E172) and magnesium stearate (E470b).

The tablet strengths are dose proportional and can be divided into two equal doses.

II.2 Drug Substance

The active substance is naproxen, an established active substance described in the European, British and United States Pharmacopoeia (Ph.Eur., BP, USP). Naproxen is a white or almost white crystalline powder. It is practically insoluble in water and soluble in ethanol (96%) and methanol. Naproxen does not exhibit polymorphism. Potential optical isomerism is possible due to a chiral centre. The produced form is the (S)-enantiomer.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additional requirement are met for residual solvents, microbiological contamination and particle size. Batch analytical data demonstrating compliance with this specification have been provided for 8 batches.

Stability of drug substance
The active substance retest period is 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. It has been adequately shown that the tablets can be divided into equal halves along the break line. The overall pharmaceutical development of the product has been adequately performed.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Naproxen Aurobindo 500 mg, tablets and reference product, Naprosyn 500 mg tablet. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. The composition of the batch used in the bioequivalence trial is identical to the final formulation chosen. *In vitro* dissolution profiles at different conditions (0.1N HCl with 0.1% sodium lauryl sulphate (SLS), pH 4.5, pH 6.8 and pH 7.4) demonstrate that the test batch is similar to the innovator product Naprosyn.

Manufacturing process
The manufacturing process consists of the following major manufacturing steps: sifting the excipients and active substance, granulation and drying, preparing the common blend, lubrication and compression. The product is manufactured using standard manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on 2 commercial batches of the common blend and 6 batches of the compressed tablets (smallest batch size) have been presented. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their respective Ph.Eur. and United States National Formulary (US-NF) monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, water, subdivision of tablets, dissolution, uniformity of dosage units, assay, related substances, thickness and microbiological contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 6 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on 6 production scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The product is stored in a clear PVC/PE/PVDC with plain Alu Blister Pack or HDPE container. Photostability studies showed that the product is photostable. Further, no specific changes or patterns were noted for any of the parameters. The proposed shelf-life of 48 months is justified. Based on the results of stability testing, the storage conditions (none) are accepted. This is in line with the ICH and European guidelines.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose, no materials of animal and/or human origin are contained or used in the manufacturing process of the medicinal product. The lactose is produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption and has been prepared without the use of other ruminant material than calf rennet.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Naproxen Aurobindo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Naproxen Aurobindo 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Naprosyn which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Naproxen 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Naproxen Aurobindo 500 mg, tablets (Aurobindo Pharma Limited, India) is compared with the pharmacokinetic profile of the reference product Naprosyn 500 mg tablets (Roche Products Limited, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The bioequivalence study was carried out on Naproxen Aurobindo 500 mg tablets. A biowaiver is requested for the tablets as per following considerations:

- Naproxen Aurobindo 250 mg and 500 mg tablets are manufactured by the same manufacturer using the same manufacturing process.
- Naproxen exhibits linear and dose proportional pharmacokinetics over the dose range of 125 mg to 500 mg.
- The qualitative composition of Naproxen Aurobindo 500 mg tablets is the same as that of the 250 mg tablets.
- Naproxen Aurobindo 500 mg tablets are dose proportional with Naproxen Aurobindo 250 mg tablets.
- The dissolution profile of Naproxen 500 mg tablets was compared to Naproxen 250 mg tablets, in different media (0.1N HCl with 0.1% SLS, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer) and was found similar. The use of surfactant in 0.1N HCl medium is justified.

Design
An open-label, balanced, randomised, single-dose, two-treatment, two-period, two-sequence, two-way crossover, comparative bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 22-45 years. 30 minutes after serving of a high fat high calorie meal, subjects received a single dose (500 mg) of one of the 2 naproxen formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The reference product is recommended to be taken with or after food. Hence, a study under fed condition is appropriate. The meal composition is in accordance with the required high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. The meal consisted of 162.2, 232.56 and 605.4 kcal from protein, carbohydrate, and fat, respectively.
The sampling scheme and frequency is adequate to estimate the pharmacokinetic parameters. Considering the half-life of 15-17 hours, a wash-out period of 7 days (i.e. at least 5 terminal half-lives to exclude carry-over effects) is agreed.

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
There were 3 drop-outs: one subject was absent for the 2nd period, one subject was withdrawn due to an adverse event (vomiting) and one subject due to personal reasons. Therefore, 33 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=33	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	1495 ± 210	1601 ± 252	71 ± 12	4.5 (2.0 - 8.0)
Reference	1447 ± 264	1555 ± 284	73 ± 13	3.5 (1.5 - 8.0)
***Ratio (90% CI)**	1.04 (1.01 - 1.08)	1.04 (1.01 - 1.06)	0.98 (0.95 - 1.01)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Naproxen Aurobindo is considered bioequivalent with Naprosyn.

The MEB has been assured that the bioequivalence study has 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).

IV.3 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 Naproxen Aurobindo.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Heart failure and myocardial infarction (MI) • Cerebrovascular accident (CVA) • Gastro-intestinal bleeding, ulceration, and perforation • Renal toxicity/renal failure • Interactions with medication that can increase the risk of bleeding and ulceration (e.g. corticosteroids, anticoagulants, SSRIs or anti-platelet agents) • Interaction with antihypertensive agents (e.g. diuretics, beta-blockers, ACE inhibitors, AT-II antagonists, etc.) • Increased toxicity in elderly • Inhibition of uterine contractions during labour prolongation of bleeding time, congenital malformations e.g. premature closure of ductus arteriosus Botalli, and renal function disorders in use during third trimester of pregnancy • Increased risk of miscarriage and embryofoetal malformations (e.g. cardiovascular, gastroschisis) in use during 1st and 2nd trimester of pregnancy
Important potential risks	• Medication Overuse Headache (MOH)
Missing information	• Off-label use of concomitant NSAIDs • Use by children <12 years of age (Naproxennatrium Aurobindo 550 film-coated tablets) • Use by children <6 years of age (Naproxen Aurobindo 250 mg and 500 mg tablets)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Naprosyn. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Meloxicam Aurobindo, UK/1135/001-002/DC. The leaflets of both products have been compared with regard to content and key messages. The bridging report submitted by the MAH has been found acceptable. The PLs are also similar in terms of lay out and writing style.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Naproxen Aurobindo 250 mg and 500 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Naprosyn 250 mg and 500 mg tablets. Naprosyn 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 Board followed the advice of the assessors. Naproxen Aurobindo was authorised in the Netherlands on 24 April 2014.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, mutually recognised the MEB's evaluation for marketing authorisation. They agreed that essential similarity has been demonstrated for Naproxen Aurobindo with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 11 April 2016.

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
New certificate from a new manufacturer (replacement of manufacturer of drug substance)	NL/H/3472/001 -002/IA/001	IA	23-5-2016	20-6-2016	Approval	No