CBG MEB

Public Assessment Report

Scientific discussion

Naproxennatrium Aurobindo 550 mg, film-coated tablets

(naproxen sodium)

NL/H/3697/001/MR

Date: 8 May 2018

This module reflects the scientific discussion for the approval of Naproxennatrium Aurobindo 550 mg, film-coated tablets. The procedure was finalised on 12 January 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Naproxennatrium Aurobindo 550 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated for use for the symptomatic treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, acute gout, acute musculoskeletal disorders and dysmenorrhoea.

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 innovator product Aleve Intense 550 mg, coated tablets (NL License RVG 14484) which has been registered in the Netherlands by Bayer B.V. since 20 November 1990.

The concerned member state (CMS) involved in this procedure was Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Naproxennatrium Aurobindo is a dark blue modified capsule shaped, film-coated tablet engraved with “T & 22” on either side of a score line on one side and with a score line on the other side.

Each tablet contains as active substance 550 mg of naproxen sodium.

The film-coated tablets are packed in PVC/Aclar-aluminium blister packs and HDPE-bottles.

The excipients are:
Tablet core - povidone (K-30) (E1201), microcrystalline cellulose (PH-200) (E460), colloidal anhydrous silica (E551), talc (E553b) and magnesium stearate (E572)
Film-coating: hypromellose 6cP (E464), titanium dioxide (E171) and macrogol/PEG 8000, FD&C blue #2/indigo carmine aluminium lacquer (E132)

II.2 Drug Substance

The active substance is naproxen sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Naproxen sodium is a white or almost white, hygroscopic, crystalline powder. The active substance is freely soluble in water, freely soluble or soluble in methanol and sparingly soluble in ethanol. Naproxen has one chiral centre. Pseudo polymorphic forms of naproxen sodium have been reported in the chemical literature. These forms are anhydrous, monohydrate, dihydrate and tetrahydrate. The MAH manufactures the anhydrous form of naproxen sodium.

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.

<u>Manufacturing process</u>
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. and CEP, with additional requirements for particle size and microbiological quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance has been provided for three full scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The stability results show no significant changes or trends in any of the tested parameters. The proposed retest period of 24 months and the proposed storage conditions 'Store in a well-closed container. Protect from light' could be granted.

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. It was aimed to create a tablet which could be considered bioequivalent to the French innovator product Apranax. The choices of the packaging materials and the manufacturing process are justified. The uniformity of tablets halves of the 550 mg tablets has been determined, using the Ph.Eur. requirements as stated in the tablets monograph. Three batches were tested. Results complied with the requirements.

A bioequivalence study has been performed using test product and the French reference product Apranax 550 mg tablets. The test product batch was manufactured using the finalised manufacturing process and composition.

Comparative dissolution profiles in different media (0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) were carried out on the batches used in the bioequivalence study. The results show that naproxen sodium tablets are practically insoluble in 0.1N HCl and pH 4.5 acetate buffer and highly soluble in pH 6.8 phosphate buffer. Calculated f_2 values (>50) demonstrated similarity between the dissolution profiles of the test and reference products.

Manufacturing process
The tablets are manufactured by means of a wet granulation procedure including preparation of the granulate, compression of lubricated blend, and coating of the compressed tablets. The manufacturing process can be regarded as a standard process and has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two minimum sized production scaled batches. Process validation on additional production scaled batches will be performed post authorisation.

Control of excipients
All excipients comply with their specifications of the Ph.Eur. For the coating material acceptable in-house specifications are provided. 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, average weight, uniformity of dosage units, water, identification, dissolution, subdivision of the tablets, assay, related substances, thickness, microbiological contamination and identification of titanium dioxide and colourants. Release and end of shelf-life specification are identical except for water content. 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 three commercial scaled 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 three full scaled batches stored at 25°C/60% RH (24 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to

the ICH stability guideline. The batches were stored in the proposed packaging. All parameters tested remained within specification limits. Photostability studies showed no sensitivity to light.
Based on the provided stability data, the proposed shelf-life of two years without special storage conditions can be granted. In-use stability for six months has been demonstrated of the drug product packaged in a HDPE container, when stored at 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Naproxennatrium Aurobindo 550 mg, film-coated tablets 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 Naproxennatrium Aurobindo 550 mg, film-coated 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Aleve 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 sodium 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 Naproxennatrium Aurobindo 550 mg, film-coated tablets (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the French reference product Apranax 550 mg tablets (Roche, France).

The choice of the reference product
The choice of the French 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.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 18-50 years. Each subject received a single dose (550 mg) of one of the two naproxen sodium formulations. After a supervised overnight fast of approximately 10 hours, subjects were provided standardised non-high-fat, pre-dose meal of 650 calories (30% fat, 52% carbohydrate and 18% proteins). After 30 minutes, subjects received a single oral dose of the assigned formulation with 240 ml of water in a randomised sequence. There were two dosing periods, separated by a washout period of eight days.

Blood samples were drawn at 0 h (pre-dose) until 70 h after administration of the products (a total of 25 time points).

The study design is accepted as this is in accordance with the 'Guideline on the Investigation of Bioequivalence'. The conduction of the study under fed condition is appropriate as it is recommended to be taken preferably during or after the meal. The composition of the meal taken before drug administration is not in accordance with the current guideline: the pre-dose meal should have been high-fat (approximately 50% of total caloric content vs. 30% in the present application) and high caloric (approximately 800 to 1000 kcal vs. 650 kcal in the present application). However, non-compliance to this requirement is acceptable as naproxen should be taken with food for safety reasons (i.e. gastrointestinal disorders) and not due to pharmacokinetic reasons (i.e. bioavailability). Moreover, the study was performed before the current guideline took effect.

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 did not check-in for the second dosing period. Therefore, 35 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of naproxen under fed conditions.

Treatment N=35	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1137 ± 245	1219 ± 307	71 ± 11	2.0± 0.8	18.2 ± 3.0
Reference	1166 ± 240	1249 ± 299	70 ± 8	2.0 ±1.0	17.8 ± 3.0
***Ratio (90% CI)**	0.97 (0.95 – 0.99)	0.97 (0.95 – 1.00)	1.00 (0.97 – 1.04)	--	--
CV (%)	5.4	5.6	9.5	--	--

$AUC_{0-\infty}$ 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*

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 Naproxennatrium Aurobindo 550 mg, film-coated tablets is considered bioequivalent with Apranax 550 mg tablets.

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 Naproxennatrium 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 embryo foetal 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, 6 years of age

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 Aleve Intense. 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 bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Naproxennatrium Aurobindo 550 mg, film-coated tablets have a proven chemical-pharmaceutical quality and is a generic form of Aleve Intense 550 mg tablets. Aleve Intense 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. Naproxennatrium Aurobindo was authorised 1 February 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Naproxennatrium Aurobindo with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 12 January 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)