CBG MEB

Public Assessment Report

Scientific discussion

Naproxen Apotex 220 mg, soft capsules

(naproxen sodium)

NL/H/3714/001/DC

Date: 20 June 2019

This module reflects the scientific discussion for the approval of Naproxen Apotex 220 mg, soft capsules. The procedure was finalised on 13 July 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
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Naproxen Apotex 220 mg, soft capsules from Apotex Europe BV.

The product is indicated for short-term treatment of:
- Headache
- Dental pain
- Muscular pain
- Lumbago
- Dysmenorrhoea
- Acute pain and fever associated with the flu and cold
- Pain and fever after vaccination

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aleve Classic 220 mg tablets (NL License RVG 19630) which has been registered in The Netherlands by Bayer BV since 22 October 1996 through a national procedure.

The concerned member states (CMS) involved in this procedure were the Czech Republic and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Naproxen Apotex is a blue transparent soft gelatin capsule containing 200 mg naproxen as 220 mg of naproxen sodium.

The soft capsules are packed in blister formed of PVDC/PE/PVC//Alu.

The excipients are
Capsule fill - macrogol 600, lactic acid, propylene glycol and povidone K30.
Capsule shell – gelatin, liquid sorbitol (partially dehydrated), glycerol, purified water and Patent blue V (E131).
Processing aids – triglyceride, isopropyl alcohol and lecithin.

II.2 Drug Substance

The active substance is naproxen sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, hygroscopic, crystalline powder. The substance is freely soluble in water, freely soluble or soluble in methanol, sparingly soluble in ethanol. Further, the substance is hygroscopic. Hydrate forms of naproxen sodium (anhydrous, monohydrate, dihydrate and tetrahydrate) are reported in the literature. However, this is not seen as critical for the proposed product.

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. and in-house requirements for the additional parameter mentioned in the CEP, as well as a parameter for particle size. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for five years 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 and function of the excipients are explained. During development composition and process parameters were optimised until the final formulation was obtained.

One bioequivalence study has been submitted. The composition of the batch used in the bioequivalence study is identical to the proposed final composition. The pharmaceutical development of the product has been adequately described and results of *in vitro* dissolution data are provided. The choice of dissolution medium for routine testing has been justified.

Manufacturing process
The manufacturing process has been sufficiently described. It involves medicine fill, gel mass preparation, encapsulation, drying and post production. Considering that the active substance is only partly dissolved at the encapsulation stage, the manufacturing is seen as a non standard process. Process validation data on the product have been presented for sufficient batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur., except for capsule shell. Acceptable in-house specifications have been provided for the capsule shell. 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 appearance, disintegration, uniformity of dosage units, identification of naproxen sodium, identification, assay, dissolution, related substances, microbial limits and hardness. The release and end-of-shelf-life specifications are identical, except the limits for disintegration, related substances and hardness. 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 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three commercial scale batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (1 month). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging material. An increase in a specified impurity was seen for all batches, however no out of specification results were obtained at long-term and intermediate conditions up to the proposed shelf-life. At accelerated conditions, only results at the initial time point are available, since due to leaking capsules in the blisters further stability testing on condition 40ºC/75% RH was stopped.

On the basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are “Do not store above 25°C”, “Do not refrigerate” and “Store in the original package in

order to protect from moisture". The results of a photostability study show that the product is significantly affected by light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatine is the only material of animal origin used. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Naproxen Apotex 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 Apotex 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 Classic 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 Naproxen Apotex 220 mg, soft capsules (Apotex Europe BV, The Netherlands) is compared with the pharmacokinetic profile of the reference product Aleve Classic (Bayer Bitterfeld GmbH, Germany).

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.

Design
A single-dose, open-label, randomised, two-treatment, two-sequence, two-period cross-over bioequivalence study was carried out under fasted conditions in 26 healthy male (n=10) and female (n=16) subjects, aged 22-54 years. Each subject received a single dose (220 mg) of one of the two naproxen sodium formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 9, 15, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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 elected to withdraw from the study for personal reasons after period 1 and was considered a drop-out from the study. Therefore 25 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	548 ± 128	593 ± 140	41.8 ± 7.3	0.78 (0.5 – 3.0)	17.3 ± 3.4
Reference	555 ± 129	606 ± 136	43.5 ± 4.9	0.75 (0.5 – 4.0)	17.3 ± 3.3
***Ratio (90% CI)**	0.99 (0.96 - 1.01)	0.98 (0.95 - 1.00)	0.95 (0.90 - 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
$t_{1/2}$ 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 Naproxen Apotex 220 mg is considered bioequivalent with Aleve Classic 220 mg.

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 Apotex.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Cardiovascular and cerebrovascular events (heart failure, MI and CVA) • Gastro-intestinal bleeding, ulceration and perforations Severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)) • Interaction with medication that can increase the risk of bleeding • Use during pregnancy and lactation • Medication overuse headache (MOH)
Important potential risks	--
Missing information	• Use by children <6 years of age (applicable for 275 mg tablets) • Use in children <12 years of age (applicable for 220 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 Aleve Classic. 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

The package leaflet has (PL) 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 test consisted of: a pilot test with four participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Naproxen Apotex 220 mg, soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Aleve Classic 220 mg soft capsules. Aleve Classic 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Naproxen Apotex with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 July 2017.

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