

Public Assessment Report

Scientific discussion

**Naproxennatrium Banner 220 mg capsules, soft
(naproxen sodium)**

NL/H/2804/001/DC

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This module reflects the scientific discussion for the approval of Naproxennatrium Banner 220 mg capsules, soft. The procedure was finalised on 3 October 2013. 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 Naproxennatrium Banner 220 mg capsules, soft from Banner Pharmacaps Europe B.V. This is a non-prescription drug.

The product is indicated for:

- 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 coated tablets (NL License RVG 19630) which has been registered in the Netherlands by Bayer B.V. since 22 October 1996.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Naproxennatrium Banner 220 mg is a blue transparent, oblong soft gelatin capsule with a double hashtag (##) print in white ink. Each soft capsule contains 220 mg sodium naproxen equivalent to 200 mg naproxen.

The capsules are packed in blisters formed of PVDC/PE/PVC//Alu or Aclar/PVC//Alu,

The excipients are:

Capsule content – macrogol; lactic acid; propylene glycol; povidone

Capsule shell – gelatin; liquid, partially dehydrated sorbitol; glycerol; purified water; patent blue V (E131)

Capsule printing - WB white NS-78-18011 (contains titanium dioxide (E171), hypromellose 2910 and purified water).

II.2 Drug Substance

The active substance is naproxen sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.).

The substance is a white or almost white, hygroscopic, crystalline powder, which is freely soluble in water, freely soluble or soluble in methanol, sparingly soluble in ethanol.

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 European Pharmacopoeia.

Manufacturing process

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

Quality control of drug substance

The drug substance specification is in line with Ph.Eur. and the additional parameters as mentioned on the CEP, as well as a parameter for particle size. The specification is considered acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 5 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 development of the product has been described, and the choice and function of the excipients are explained. During development the composition and process parameters were optimised until the final formulation was obtained. 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 involves the following steps: medicine fill, gel mass preparation, encapsulation and drying. The manufacturing process has been sufficiently described. Details concerning bulk stability have been provided. The manufacturing is seen as a non standard process. Sufficient process validation data of several production-scale batches has been provided.

Control of excipients

The excipients comply with the Ph.Eur., except for Opacode WB white NS-78-18011, Patent blue and lecithin. Acceptable in-house specifications have been provided for these ingredients.

Quality control of drug product

The product specification includes tests for appearance, disintegration, uniformity of dosage units, identification of naproxen sodium, identification of Patent blue V, 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. The drug product specification is acceptable and all limits have been adequately justified.

The analytical methods have been adequately described and validated. Batch analytical data from three commercial-scale batches has been provided; all batches comply with the proposed release specification.

Stability of drug product

Stability data on the product has been provided for three commercial-scale batches stored at 25°C/60% RH (12 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 (Triplex and Aclar blisters).

No out-of-specification results were obtained at long-term and intermediate conditions. Photostability studies showed that the product is not sensitive to light.

Based on the stability data provided and the nature of the drug product (*i.e.* gelatin capsules), the following storage conditions should be applied: "Do not store above 30°C", "Do not refrigerate" and "Store in the original package in order to protect from moisture". A shelf-life period of 15 months can be granted based on the provided data.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The only excipient of animal origin, gelatine, is obtained by the partial hydrolysis of collagen produced from bones of animals. CEPs have been provided for the suppliers of gelatine, showing that this material is produced in-line with current requirements concerning the minimisation of transmission of BSE/TSE.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Naproxennatrium Banner 220 mg soft capsules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to finish the on-going stability studies.
- The MAH committed to place two additional commercial-scale batches on stability testing.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Naproxennatrium Banner 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Naproxennatrium Banner 220 mg soft capsules (Banner Pharmacaps Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Aleve 220 mg tablets (Bayer Bitterfeld GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy (10 males/16 females) subjects, aged 22-54 years. Each subject received a single dose (220 mg) of one of the 2 naproxen sodium formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.50, 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. The procedures followed for a fasting condition and a wash-out period of 7 days (*i.e.* at least 5 terminal half-lives to exclude carry-over effects) is agreed. Naproxen may be taken without reference to food intake, although it is preferably taken with food. Food reduces the rate but not the extent of absorption. A food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence

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 withdrew for personal reasons. The remaining 25 subjects were included in the analysis.

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

Treatment N=25	AUC_{0-t} µg.h/ml	AUC_{0-∞} µg.h/ml	C_{max} µg/ml	t_{max} h	t_{1/2} h
Test	548 $\pm$ 128	593 $\pm$ 140	41.8 $\pm$ 7.3	0.78 (0.5 – 3.0)	--
Reference	555 $\pm$ 129	606 $\pm$ 136	43.5 $\pm$ 4.9	0.75 (0.5 – 4.0)	--
*Ratio (90% CI)	0.99 (0.96 – 1.01)	0.97 (0.95 – 1.00)	95 (0.90 – 1.01)	--	--
CV (%)	--	--	--	--	--
AUC_{0-∞} 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					

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Naproxennatrium Banner 220 mg soft capsules is considered bioequivalent with Aleve 220 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 Clinical safety

The use of lactic acid in this medicinal product is considered safe and acceptable, considering the neutral pH of the fill, the unlikelihood that the capsules will burst, the removal of lactic acid by water or milk in case a capsule would burst in the oesophagus, the acceptance of lactic acid as food additive according to Regulation 1333/2008, without a maximum level as described in Directive 95/2/EC, the “not specified” acceptable daily intake (“will not represent a hazard to health”), the low daily intake as compared to the intake as a result of food and the non-chronic use of this medicinal product.

IV.4 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 Banner capsules.

Summary table of safety concerns as approved in RMP

Important identified risks	Allergic conditions Cardiovascular and cerebrovascular events Coagulation disorders Gastrointestinal disorders Renal disorders
Important potential risks	Fertility Hepatic disorders Skin and subcutaneous tissue disorders
Missing information	Pregnancy and lactation Exposure in children below 12 years of age

Routine pharmacovigilance activities in conjunction with appropriate product labelling are considered adequate risk minimization measures. No additional measures are required.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aleve tablets. 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 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 4 participants, followed by two rounds with 10 participants each. The questionnaire contained 19 questions specific both to the medicinal product, addressing the key safety issues and concerns of the product, and to the format of the package leaflet. 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

Naproxennatrium Banner 220 mg capsules, soft has a proven chemical-pharmaceutical quality and is a generic form of Aleve Classic 220 mg coated tablets. 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 Naproxennatrium Banner 220 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 October 2013.

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