PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Naproxennatrium Nordic 550 mg, film-coated tablets
Nordic Pharma B.V., the Netherlands

naproxen sodium

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB. It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation. This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 104339

14 November 2012

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non steroids; propionic acid derivatives
ATC code: M01AE02
Route of administration: oral
Therapeutic indication: rheumatic pain; muscular pain; back pain
Prescription status: non prescription
Date of authorisation in NL: 2 June 2010
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Naproxennatrium Nordic 550 mg, film-coated tablets from Nordic Pharma B.V. The date of authorisation was on 2 June 2010 in the Netherlands.

The product is indicated for:
- rheumatic pain
- muscular pain
- back pain

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

Naproxen has been shown to have anti-inflammatory, analgesic and antipyretic properties when tested in classical animal test systems. It exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis. It inhibits prostaglandin synthetase, as do other non-steroidal anti-inflammatory agents. As with other agents, however, the exact mechanism of its anti-inflammatory action is not known.

This national 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 (original product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Apranax 550 mg tablets, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is naproxen sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is soluble in water and methanol and sparingly soluble in alcohol. Naproxen has one chiral centre. No polymorphic forms are known.

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 the Ph.Eur. with two additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for several production size batches stored at 25°C/60% RH for 60 months and 40°C/75% RH for 6 months. The stability results show that no variability or change at accelerated or long-term storage conditions. The proposed retest period of 5 years is therefore justified.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Naproxen sodium Nordic 550 mg is a white oval film-coated tablet, scored on both sides. The tablet can be divided into equal halves.

The film-coated tablets are packed in PVC/PVDC/Alu-blisters.

The excipients are: povidone (E1201), microcrystalline cellulose (E460), silicon dioxide (E551), magnesium stearate (E572), talc (E553b), hypromellose (E464), titanium dioxide (E171), macrogol.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The quantitative composition of the Italian (Synflex® Forte) and French brand leader (Apranax® Roche) products were used as a basis for the development of the generic tablet. Different core formulations of the test product were prepared. Comparative dissolution studies were performed with brand leader products such as the French product Aparanax, the Spanish product Antalgin and the Finnish product Miranax. The test product and reference product (Apranax) that were used in the bioequivalence study have been indicated. The quantitative formulations are similar with the exception that the test product contains silicon dioxide and no yellow colouring. The choice of reference product used in the bioequivalence study and its relevance for the Dutch market has been demonstrated. A comparative dissolution profile has been included. The profile shows that the biostudy batch is comparable to the Dutch reference product. Breakability results were obtained using the Ph.Eur. tablet monograph. Subdivided parts complied with the test for Uniformity of mass of single preparations (Ph.Eur. 2.9.5). The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The granulate is produced in two sub-batches of equal size. The materials are mixed and the granulation fluid then sprayed onto the powder, followed by drying of the wet granulation. The two granulation batches are then blended and compressed, followed by coating and packing. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four production-size batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the European Pharmacopoeia, with the exception of silicon dioxide which conforms to the USP/NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, uniformity of dosage units, subdivision of tablets, height, hardness, identification of naproxen and sodium, assay, related substances, disintegration, dissolution, microbial purity, water content, and identification of titanium dioxide. With the exception of the limit for water content, the release and shelf-life requirements/limits are identical, The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on four full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for four production-size batches stored at 25°C/60% RH (48 months for 3 unscored batches and 24 months for 1 scored batch), 30°C/65% RH (12 months) and 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 PVC/PVDC-Alu blister strips. At all storage conditions a slight increase in average mass of the tablets was observed, but all results remained within specification and no significant changes in any of the other parameters were observed at any of the storage conditions. The drug product is not stable with respect to light when stored in a transparent blister packaging. The drug product is stable with respect to light when stored in the opaque blister packaging.
Based on the submitted stability data, it was concluded that the claimed shelf-life of 5 years is justified together with the proposed storage conditions of "Store in the original package in order to protect from light" for the commercial packaging.

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.2 Non-clinical aspects

This product is a generic formulation of Aleve, which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of naproxen sodium released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Naproxennatrium Nordic 550 mg (Nordic Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Apranax® 550 mg tablets (Roche, France).

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

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 fasted conditions in 26 healthy male and female subjects, aged 20-51 years. Each subject received a single dose (550 mg) of one of the 2 naproxen sodium formulations. The tablet was orally administered with 200 ml water after overnight fasting for 10 hours. There were 2 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2.00, 2.50, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours after administration of the products.

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 no drop-outs. All subjects included in the study were used for statistical evaluation.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-4} )</th>
<th>( \text{AUC}_{0-\infty} )</th>
<th>( \text{C}_{\text{max}} )</th>
<th>( t_{\text{max}} )</th>
<th>( t_{1/2} )</th>
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The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( \text{C}_{\text{max}} \) are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of naproxen sodium under fasted conditions, it can be concluded that Naproxennatrium Nordic 550 mg and Apranax® 550 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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.

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).

**Risk management plan**
Naproxen was first approved in 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of naproxen can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

**SPC**
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Aleve Intense.

**Readability test**
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 two rounds with 10 participants each. Twelve standard practical questions were asked. Results of the first round of testing were good overall. For all items at least 90% scored well on the diagnostic questions. After the first test round no critical issues could be identified, therefore the package leaflet did not need to be changed. Results of the second round of testing confirmed the results of the first test round. At least 90% of the respondents...
scored well on all of the diagnostic questions. In both test rounds respondents were asked 16 questions with respect to layout. For all items at least 95% scored not good/not bad, good or very good. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Naproxennatrium Nordic 550 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Aleve Intense 550 mg. Aleve is a well-known medicinal product with an established favourable efficacy and safety profile. Naproxennatrium Nordic is available at pharmacies only. This is in accordance with the reference product Aleve 550.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Naproxennatrium Nordic 550 mg, film-coated tablets was authorised in the Netherlands on 2 June 2010.

There were no post-approval commitments made during the procedure.
# List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>$C_{\text{max}}$</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>$t_{1/2}$</td>
<td>Half-life</td>
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<tr>
<td>$t_{\text{max}}$</td>
<td>Time for maximum concentration</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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