COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Nuralgan 500 mg/200 mg, film-coated tablets

(paracetamol/ibuprofen)

NL/H/4888/001/DC

Date: 1 August 2022

This module reflects the scientific discussion for the approval of Nuralgan 500 mg/200 mg, film-coated tablets. The procedure was finalised at 15 March 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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 Nuralgan 500 mg/200 mg, film-coated tablets, from Laboratoires S.M.B. S.A.

The product is indicated in adults for the short-term symptomatic treatment of mild to moderate pain. This product is especially suitable for pain which requires stronger analgesia than ibuprofen or paracetamol alone.

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 European reference products (ERP) Nuromol 200 mg/500 mg film-coated tablets, which have been registered in Poland since 1 December 2010 by Reckitt Benckiser.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Luxembourg, Portugal, Spain and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Nuralgan is a white to off-white oblong film-coated tablet. Each tablet contains paracetamol 500 mg and ibuprofen 200 mg.

The film-coated tablets are packed in opaque white PVC/PVDC-Al blister or opaque white PVC/PVDC-Al perforated unit dose blisters for hospital use.

The excipients are:
Tablet core - povidone (E1201), microcrystalline cellulose, sodium starch glycolate and magnesium stearate
Tablet coating - polyvinyl alcohol , macrogol, talc (E553b) and titanium dioxide (E171).

II.2 Drug Substances

The active substances are paracetamol and ibuprofen, both established active substances described in the European Pharmacopoeia (Ph.Eur.).

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.

Paracetamol

Paracetamol is a white or almost white, crystalline powder. It is sparingly soluble in water, freely soluble in ethanol (96 per cent), very slightly soluble in methylene chloride. Paracetamol does exhibit polymorphism. There are three known polymorphs of paracetamol: a stable monoclinic form, a metastable orthorhombic form and an unstable uncharacterised form. The manufacturer ensures consistently providing the stable monoclinic form and control of the polymorphic form can be excluded from the control strategy.

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. An additional test for particle size has been included. Batch analytical data demonstrating compliance with this specification have been provided for five 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.

Ibuprofen

Ibuprofen is a white or almost white, crystalline powder or colourless crystals. It is practically insoluble in water, freely soluble in acetone, in methanol, and in methylene chloride. It dissolves in dilute solution of alkali hydroxides and carbonates. At least two polymorphic forms of ibuprofen are known in the literature, one of them being metastable and only generated in specific conditions. There is therefore no need for solid state identification in the drug substance specifications.

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 CEP. An additional test for particle size has been included. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

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 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. Quality by design aspects have been applied throughout the development of the drug product. No design space has been claimed. The choices of the packaging and manufacturing process are considered justified. One bioequivalence study has been performed. Dissolution studies showed that the test product and reference product have comparable dissolution profiles. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consist of manufacturing of a intermediate through spray drying, blending, lubrication, tableting, coating and packaging and has been validated according to relevant European guidelines. Process validation data on the product have been presented for one pilot and two production batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. requirements except for the Opadry coating. In-house specifications have been provided for the coating and are acceptable. The method description and validation for the in-house particle size procedure for sodium starch glycolate have been 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 appearance, uniformity of dosage units, identification of both active substances, assay of both active substances, related substances for both active substances, dissolution of both active substances and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from one pilot and two production 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 batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in accordance with the ICH stability guideline. The batches were stored in a PVC/PVdC-aluminium blister. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 3 years. This medicinal product does not require any special storage conditions.

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 Nuralgan 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 Nuralgan 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 Nuromal 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

Paracetamol and ibuprofen are well-known active substances 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Nuralgan 500 mg/200 mg, film-coated tablets (Laboratoires S.M.B. S.A., Belgium) is compared with the pharmacokinetic profile of the reference product Nuromol 200 mg/500 mg film-coated tablets (Reckitt Benckiser, Poland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference product 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 fed conditions in 40 healthy male and female subjects, aged 20-54 years. Each subject received a single dose (500 mg paracetamol/200 mg ibuprofen) of one of the 2 paracetamol/ibuprofen formulations. The tablet was orally administered with 240 ml water after high fat, high caloric meal (two eggs fried in butter, two strips of bacon, two slices of toast with butter, hash brown potatoes and whole milk).

Blood samples were collected at pre-dose and at 10, 20, 30, 45 min and at 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8, 12 and 24 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC of the applied product, to minimise side effects, it is recommended that patients take the tablet with food.

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
All 40 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=40	AUC_{0-t} (µg.h/ml)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	21.5 ± 6.8	22.3 ± 6.8	5.8 ± 2.0	1.25 (0.5 – 2.75)	3.6 ± 1.6
Reference	22.0 ± 6.7	22.9 ± 6.9	5.7 ± 1.6	1.25 (0.5 – 4.0)	3.8 ± 1.8
***Ratio (90% CI)**	0.98 (0.94 – 1.01)	--	1.01 (0.94 – 1.08)	--	--
CV (%)	10.1	--	19.6	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ibuprofen under fed conditions.

Treatment N=40	AUC_{0-t} (µg.h/ml)	$AUC_{0-\infty}$ (µg.h/ml)	C_{max} (µg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	45.6 ± 8.8	48.0 ± 9.0	13.9 ± 4.2	1.5 (0.5 – 6.0)	1.9 ± 0.3
Reference	45.9 ± 9.5	49.2 ± 10.1	13.7 ± 3.7	1.5 (0.75 – 4.0)	2.0 ± 0.5
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	--	1.01 (0.92 – 1.12)	--	--
CV (%)	7.9	--	26.0	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Nuralgan is considered bioequivalent with Nuromol.

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 Nuralgan.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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 Nuromol. 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 (PL) 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, 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Nuralgan 500 mg/200 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Nuromol 200 mg/500 mg film-coated tablets. Nuromol 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 Nuralgan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 March 2022.

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