

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Paracetamol Nordic 500 mg, granules
Nordic Pharma B.V., the Netherlands**

paracetamol

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 and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

**EU-procedure number: NL/H/1765/001/DC
Registration number in the Netherlands: RVG 105788**

22 September 2011

Pharmacotherapeutic group:	other analgesics and antipyretics: anilides
ATC code:	N02BE01
Route of administration:	oral
Therapeutic indication:	Symptomatic treatment of mild to moderate pain and/or fever
Prescription status:	non prescription
Date of authorisation in NL:	27 June 2011
Concerned Member States:	Decentralised with BE, DE, DK, FI, FR, IT, NO, SE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

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 member states have granted a marketing authorisation for Paracetamol Nordic 500 mg, granules from Nordic Pharma B.V. The date of authorisation was on 27 June 2011 in the Netherlands.

The product is indicated for symptomatic treatment of mild to moderate pain and/or fever in adults and adolescents only.

The maximum daily dose according to the SPC is 3000 mg in adults.

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

Paracetamol has both analgesic and antipyretic effects. However, it does not have an anti-inflammatory effect.

This decentralised procedure concerns a hybrid application with a change in pharmaceutical form. Paracetamol Nordic 500 mg is formulated as granules, whereas the reference product Panadol 500 mg is an immediate release tablet. Oral paracetamol has been marketed in Europe for more than 50 years, mostly as conventional immediate release tablets containing 500 mg paracetamol. In the Netherlands, Panadol Gladde Tablet 500 mg, tablets has been registered by GlaxoSmithKline Consumer Healthcare B.V. since 1995 (NL License RVG 18550). The product was first authorised in NL in 1956. In addition, reference is made to Panadol authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) 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 Panadol Gladde tablet 500 mg, registered in the Netherlands. 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 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.

No paediatric development programme has been submitted, as this is not required for substitutional products.

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 paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder, which is sparingly soluble in water. Paracetamol does not have chiral centres and exists as three polymorphic forms. One polymorphic form is used.

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 new 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 and the CEP, with additional requirements for particle size. The specification is acceptable in view of various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale 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.

* *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

Paracetamol Nordic 500 mg are white to off- white, freely flowable granules.

The product is packed in cartons containing PETP/Alu/PE sachets.

The excipients are: basic butylated methacrylate copolymer, colloidal hydrated silica (E551), stearic acid, sodium laurilsulfate, xylitol (E967), saccharin sodium (E954), aspartame (E951), grapefruit flavour (containing potato maltodextrin, acacia gum (E 414), butylhydroxyanisole (E 320)).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The objective was to develop a very rapid dissolution profile with acceptable organoleptic characteristics. This was achieved by developing microencapsulated paracetamol. The optimal granular grade of paracetamol was established. The dissolution profile of drug product obtained

with varying percentages of coating was measured at various pH values. The dissolution profile of Paracetamol Nordic was compared to Panadol 500 mg tablets obtained from several EEA countries. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing consists of four production steps: microencapsulation of paracetamol, mixing blend 1, mixing blend 2, preparing the final blend (granules) and packaging. The manufacturing process is considered a non-standard process due to the microencapsulation process.

The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. and adequate in-house specifications. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, dissolution, degradation, moisture, uniformity of dosage units and microbial purity. The shelf-life requirements are identical to the release specification. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on two validation batches at commercial scale, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for the two commercial-scaled validation batches stored at 25°C/60% RH and 40°C/75% RH for up to 18 months. The conditions used for the commercial packaging in the stability studies are according to the ICH stability guideline.

The results over the limited period do not show out-of-specifications or significant trends. However, the stability results are based on the old composition, therefore, the batches can be tentatively used as supporting batches and extrapolation is not allowed. Based on the identical packaging and the similarity between the compositions, a shelf life of 18 months can be granted. No specific storage condition is required. The packaging material is a high barrier laminate against moisture, light and oxygen.

The MAH committed to start stability testing on three commercial-scale batches of the current formulation.

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 active substance has been available on the European market for over 50 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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 paracetamol 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

Paracetamol is a well-known active substance with established efficacy and tolerability.

The MAH discussed the possibility for a biowaver, but eventually decided to submit a bioequivalence study for this hybrid application. In the bioequivalence study the pharmacokinetic profile of the test product Paracetamol Nordic 500 mg, granules (Nordic Pharma B.V., the Netherlands) is compared with the

pharmacokinetic profile of the reference product Panadol 500 mg film-coated tablets (GlaxoSmithKline B.V., the Netherlands).

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 subjects (13 males/13 females), aged 19-48 years. Just before test product administration the subjects received and swallowed 20 mL of water to wet the mouth. The medication (1000 mg, two single-dose packs containing granules of the test product or two tablets of the reference product) was administered orally to each subject. The test product was administered at the back of the tongue and swallowed without water while the reference product was administered with 200 mL of water. Immediately after administration, the subject's oral cavity and hands were checked to confirm complete medication and fluid intake. Two hours after dosing the subjects were allowed to drink 200 ml and breakfast was used 4 hours upon dosing. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.0, 3, 4, 6, 8, 12, 16, and 24 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

One subject was withdrawn before the second period due to adverse event (tonsillitis). The remaining 25 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=25	AUC _{0-t} ug.h/ml	AUC _{0-∞} ug.h/ml	C _{max} vg/ml	t _{max} h	t _{1/2} h
Test	51.9 \pm 13.8	53.0 \pm 14.2	14.3 \pm 5.1	1.0 (0.3 – 2.0)	4.4 \pm 1.5
Reference	50.3 \pm 12.8	51.1 \pm 13.3	16.1 \pm 6.3	0.5 (0.3 – 2.0)	4.2 \pm 1.3
*Ratio (90% CI)	1.03 (0.99 – 1.07)	--	0.90 (0.81 – 1.00)	--	--
CV (%)	9.0	--	21.7	--	--
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*

The 90% confidence intervals calculated for AUC_{0-t} and C_{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 paracetamol under fasted conditions, it can be concluded that Paracetamol Nordic 500 mg, granules and Panadol 500 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Paracetamol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of paracetamol. Therefore, 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

There is now more than 50 years post-authorisation experience with the active substance paracetamol. The safety profile of paracetamol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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 decentralised procedure is in accordance with those accepted for other paracetamol products.

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 a pilot test with 5 participants, followed by two rounds with 10 participants each. Fourteen questions were asked. The number of correctly answered questions was sufficient, although one question was answered correctly by 8 out of 10 participants. This 80% is considered acceptable, as changing the PIL would affect the QRD template in this case, which is not recommended.

Overall, in both test rounds 97% of the requested information was found and understood. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol Nordic 500 mg, granules has a proven chemical-pharmaceutical quality and is a hybrid form of Panadol 500 mg film-coated tablets. Panadol 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other paracetamol containing products.

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 Paracetamol Nordic 500 mg, granules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 19 January 2011. Paracetamol Nordic 500 mg, granules was authorised in the Netherlands on 27 June 2011.

A European harmonised birth date has been allocated and subsequently the first data lock point for paracetamol is May 2012. The first PSUR will cover the period from January 2011 to May 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 31 January 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to start stability testing on three commercial-scale batches of the current formulation.

List of abbreviations

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

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