CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Paracetamol Ratiopharm 500 mg and 1000 mg tablets
Ratiopharm Nederland 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/1980/001- 002/DC
Registration number in the Netherlands: RVG 107336-7

22 September 2011

Pharmacotherapeutic group:	other analgesics and antipyretics
ATC code:	N02BE01
Route of administration:	pharmacy only
Therapeutic indication:	symptomatic treatment of mild to moderate pain and/or fever
Prescription status:	non-prescription
Date of authorisation in NL:	26 July 2011
Concerned Member States:	Decentralised procedure with BG, PL (both strengts); DE, ES, FI, LU, NO and PT (only 1000 mg); and SE (only 500 mg)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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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 Ratiopharm 500 mg and 1000 mg tablets, from Ratiopharm Nederland B.V. The date of authorisation was on 26 July 2011in the Netherlands. The product is indicated for the symptomatic treatment of mild to moderate pain and/or fever. For use in adults, adolescents and children from the age of 4 years, the 1000 mg tablets only for adults and adolescents from the age >16 years.

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 generic application claiming essential similarity with the innovator products Panodil 500 mg and 1000 mg tablets which have been registered in Norway by Glaxo Smith Kline since 1977 (original product). In addition, reference is made to Panodil authorisations in the individual member states (reference 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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Panodil 1000 mg tablets, registered in Norway. 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, as this is not required for generic medicinal 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

General information
The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph. Eur.*). The active substance is sparingly soluble in water. For the drug substance the MAH uses the CEP procedure.

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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
This is covered by the CEP.

Quality control of drug substance
Specific information, other than references to the CEPs, for the drug substance is not included by the MAH. It is imposed on the applicant to lay down the requirements of the Ph.Eur. monograph of paracetamol as drug substance specification.

Stability of drug substance
For the drug substance from one manufacturer reference is made to CEP. On the CEP a re-test period of five years when adequately stored is mentioned.
For material obtained from the other manufacturer the MAH has provided stability data of the drug substance. Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (60 months) and for three full-scale batches stored at 40°C/75% RH (6 months). The batches were adequately stored. All parameters remain relatively stable at both conditions. The proposed re-test period of 5 years and the storage condition '*Store protected from light*' were granted.

** 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
The product at issue is an uncoated tablet containing 500 or 1000 mg paracetamol as active substance. As excipients povidone, croscarmellose natrium, maize starch, talc, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate and purified water are used. The excipients and packaging are usual for this type of dosage form. The tablets are packaged in opaque PVC/Alu blisters or HDPE bottles. The excipients and packaging are common for this type of product.

The composition of the 500 mg is fully dose proportional to the 1000 mg strength.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the tablets is identical to an existing tablet marketed in Germany. The tablets are manufactured from a granulate that contains all the excipients. The granulate is manufactured according to the applicants composition by the two manufacturers of the drug substance. The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The BE batch is of sufficient size in relation to the intended commercial batch size. The BE study was performed against the Norwegian reference product. The MAH has demonstrated that the reference product used in the bioequivalence study is comparable to the Dutch reference product, and the reference products of the other member states involved in the procedure, in terms of dissolution characteristics (at pH 1.2, 4.5 and 6.8).
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
Intermediate product
The manufacturing process of the granulate consists of dry mixing, wet granulation, sifting and blending. Both manufacturers apply the same process for this intermediate product. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the intermediate has been presented for three full-scale batches of granules. The product is manufactured using conventional manufacturing techniques.
Both manufactures of the intermediate and the MAH have included adequate specifications for the intermediate product. The product specification for the granulate includes tests for description, identification for paracetamol and three excipients, related substances, loss on drying and assay.
Both manufacturers of the granulate have included stability data of several commercial batches stored under ICH conditions that demonstrated that the granulate remains stable when stored in a PE bag in a fibre drum for 3 years or 5 years without specific storage conditions.

Tabletting
The manufacturing process of the tablets consists of homogenisation and compression. The manufacturing process for both tablet strengths has been adequately validated according to relevant European guidelines. Process validation data for the 500 mg tablets has been presented for 3 full-scale batches. Process validation for full-scale batches of the 1000 mg tablets will be performed post authorisation. Since the product is manufactured using conventional manufacturing techniques and consists for approximately 77% of the drug substance this is acceptable.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification for the tablets includes tests for description, average mass, resistance to crushing, uniformity of mass of tablets halves, friability, dissolution, loss on drying, identification for paracetamol, related substances, uniformity of dosage units, assay and microbiological purity.
The release and end of shelf-life specification limits are identical with the exception of loss on drying. The specification is considered acceptable.
The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on 6 production scale batches of the 500 mg strength and 4 batches of a specific size for tablets of the 1000 mg strength, demonstrating compliance with the release specification.

Breakability
The 500 and 1000 mg tablets contain a score-line. During stability testing, for the 500 mg tablets a temperature dependant increase in tablet hardness was observed. Breakability at these high hardness values therefore needed to be demonstrated. The MAH has tested a batch of 500 mg tablets with an adequate average hardness for compliance to the Ph.Eur. requirements for uniformity of mass of tablets halves. The results demonstrate compliance to the Ph.Eur. It is therefore concluded that higher values of hardness of the 500 mg tablets do not affect the breakability.

Container closure system
The proposed packaging materials are an opaque PVC/Alu-Pergamin blister or HDPE bottles. A child-proof container closure system is not claimed in the SPC, so the blisters and HDPE containers do not need to comply with NEN-ISO 14375:2003 for child proof system.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. Microbiological testing is performed on the finished product according to the Ph.Eur. general text 5.1.4 Microbiological quality of pharmaceutical preparations.

Stability tests on the finished product
Stability data on the product has been provided for 6 commercial-scale batches of the 500 mg and 4 pilot-scale batches of the 1000 mg batches stored at 25°C/60%RH (up to 60 months) and 30°/70%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-aluminium blisters and HDPE containers. In the 500 mg tablets a temperature dependant increase in tablet hardness was observed. Breakability at these high hardness values was successfully demonstrated. All other parameters remained stable throughout the storage period for both tablet strengths and all temperatures.
The proposed shelf-life of 5 years for the 500 mg and 2 years for the 1000 mg product and the proposed storage condition '*No special storage conditions*' are justified.
The in-use stability of the drug product was examined by storing the drug product in an open container at 25°C/60%Rh for a period of 6 months. All parameters remained stable and an in-use storage claimed is not deemed necessary.

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 Panodil, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Paracetamol Ratiopharm 1000 mg tablets (Ratiopharm Nederland B.V., the Netherlands) are compared with the pharmacokinetic profile of the reference product Panodil 1000 mg tablets (GSK, Norway).

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 (if applicable) 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 centre, randomized, single dose, laboratory-blinded, 2-period, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male and female volunteers. When applicable, an overview of concomitant medications was provided for a subject. After a supervised overnight fast, a single dose of the assigned formulation was administered in the morning. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

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.

Results
Thirty-eight subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1 and day 8. There were 4 drop-outs: two subjects were withdrawn from the study before dosing of period 2 and prior to plasma analysis, given that he has missed the 20 minutes blood sample collection during period 1; and one subject withdrew consent before dosing of period 2 for personal reasons; one subject was withdrawn from the study before dosing of period 2 due to positive drug test (cocaine).
Finally, thirty seven subjects were considered in the statistical analysis, because one subject was withdrawn from the statistical analysis following sample analysis due to pre-dose concentration greater than 5% of the acetaminophen C_{max} detected for both periods. Samples collected in periods 1 and 2 for this subject were analyzed but later excluded from the statistical analysis.
One subject was included in the statistical analysis only for the C_{max} and T_{max} parameters and the terminal phases of paracetamol (acetaminophen) were not estimated for this subject for both periods.

Eighteen (18) of the forty-two (42) subjects experienced a total of twenty-nine (29) adverse events during the study. Sixteen (16) adverse events (8 different types) were reported after the single dose administration of the Test product and eighteen (18) adverse events (10 different types) were reported after the single dose administration of the Reference product. Five (5) adverse events (2 episodes of blood potassium increased and 1 episode of each white blood cell count increased, alanine amino-transferase increased, aspartate amino-transferase increased) associated with post-study laboratory test results were imputed to both formulations. No serious adverse events (SAEs) were recorded in this study.

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

Treatment N = 37	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	60.5 ± 18.9	61.7 ± 19.4	17.3 ± 4.4	0.67 (0.33 – 1.5)	4.6 ± 1.5
Reference	61.6 ± 20	62.8 ± 20.4	18.7 ± 5.9	0.67 (0.33 – 3)	4.4 ± 1.23
***Ratio (90% CI)**	98.6 (96.0 – 101.4)	98.7 (96.1 – 101.4)	94.2 (88.5 – 100.4)	---	---
CV (%)	6.8	6.8	16.2	---	---

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ 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 Ratiopharm 1000 mg tablets and the Panodil 1000 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results to 500 mg strength
The 500 mg tablet is dose-proportional with the 1000 mg tablet for which bioequivalence was shown. The tablets have been manufactured by the same manufacturing process. In addition, paracetamol shows linear pharmacokinetics. Dissolution profiles were submitted, at a pH of 1.2, 4.5, 5.8 and 6.8. Dissolution was > 85% within 15 minutes, indicating that the Test formulation is an immediate release formulation. The results of the bioequivalence study performed with the 1000 mg tablets therefore also apply to the 500 mg strength.

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
Paracetamol was first approved in 1977, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of paracetamol 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

Readability test

The the MAH applied for an exemption to perform a readability test on the package leaflet. The MAH stated that the Paracetamol ratiopharm package leaflet is almost identical to the registered package leaflet of procedure DE/H/1478/001/MR (Parecetamol-ratiopharm® 500) and a tested layout is used. The MAH provided a bridging report in which the differences and similarities in the key messages are discussed. Therefore, the MAH applied for an exemption to perform a readability test on the package leaflet of the paracetamol ratiopharm NL/H/1980/001-002/DC. This proposal is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol Ratiopharm 500 mg and 1000 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Panodil 500 mg and 1000 mg tablets. Panodil is a well-known medicinal product with an established favourable efficacy and safety profile. The prescription status for paracetamol is in all member states non prescription. In the Netherlands the 500 mg tablet is additionally for general sale, the 1000 mg is only pharmacy only.

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.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Paracetamol Ratiopharm 500 mg and 1000 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 27 May 2011. Paracetamol Ratiopharm 500 mg and 1000 mg tablets are authorised in the Netherlands on 26 July 2011.

The first PSUR will be submitted in July 2012 with DLP May 2012. Thereafter PSURs will be submitted in 3-yearly intervals or immediately upon request.

The MAH proposes early renewal submission in Jul 2012 with common renewal date Jan 2013. This is acceptable.

The following post-approval commitments have been made during the procedure:

Quality - active substance
- It is imposed on the MAH to lay down the requirements of the Ph.Eur. monograph of paracetamol as drug substance specification.

Quality - medicinal product
- Process validation of the manufacturing process for full-scale batches of the 1000 mg tablets will be performed post authorisation.

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
$t_{½}$	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