CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Paracetamol PharmaMatch 1000 mg, tablets
Pharmamatch 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.
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 107223

30 August 2011

Pharmacotherapeutic group:	other analgesics and antipyretics: anilides
ATC code:	N02BE01
Route of administration:	oral
Therapeutic indication:	mild to moderate pain associated with arthrosis of the hip or knee
Prescription status:	prescription only
Date of authorisation in NL:	10 November 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 Paracetamol PharmaMatch 1000 mg, tablets from Pharmamatch B.V. The date of authorisation was on 10 November 2010 in the Netherlands.

The product is indicated for the management of mild to moderate pain associated with arthrosis of the hip or knee in adults and adolescents only. The maximum daily dose according to the SPC is 4000 mg.

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. The effect appears to involve inhibition of the enzyme prostaglandin synthetase, but just the lack of an anti-inflammatory effect can not be explained by this. It is possible that the distribution of paracetamol throughout the body and thus the place where the inhibition of prostaglandin synthetase takes place may be involved. The advantage of paracetamol is that a number of adverse effects characteristic of NSAIDs are entirely or mostly absent for paracetamol. Therefore, paracetamol is a good alternative to NSAIDs for the treatment of pain.

Paracetamol is an old and established substance, a very well known analgesic, and available as over-the-counter product throughout Europe. Paracetamol (acetaminophen) was introduced in 1893 by von Mering.

This national procedure concerns a generic application claiming essential similarity with the reference product Panadol 1000 mg Artrose tablets (NL License RVG 26161), registered in the Netherlands by GlaxoSmithKline Healthcare B.V. since 11 December 2000 for the same therapeutic indication.

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. The current application does not include a comparative bioavailability or bioequivalence study, but reference is made to fulfilling all requirements for a biowaiver. See paragraph II.3 “Clinical Aspects”. 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 a generic application.

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 sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. The molecule does not contain a chiral centre and only one grade of polymorphic form.

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. monograph, with appropriate additional requirements. The specification is acceptable in view of the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 5 production-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 PharmaMatch 1000 mg is a white to off-white, caplet-shaped tablet, debossed with scoreline between “10” & “00” on one side and scoreline between “PA” & “RA” on other side. The tablet can be divided into equal halves.

The tablets are packed in PVC/Alu blisters.

The excipients are: povidone K30 (E1201), pregelatinised maize starch, sodium starch glycolate, stearic acid (E570).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The packaging is common for this kind of dosage form.

Since paracetamol is eligible for a biowaiver no bioequivalence study was performed. Comparative dissolution profiles have been included. Dissolution profiles of the reference product and three batches of test product were established in four different dissolution media. The drug release was found to be over 85% after 15 min. for all batches and all dissolution media. Therefore it has been demonstrated that the dissolution profiles of reference and test products are similar over the entire physiological pH range in accordance with the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence.*
Breakability has been demonstrated for the product. Subdivision of tablets is included as a parameter in the finished product specification.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of two steps: wet granulation and compression. The manufacturing process is considered standard and has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for five full scaled batches and three pilot-scale batches. The product is manufactured using conventional manufacturing techniques. The proposed maximum batch size is acceptable.

Control of excipients
All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identity, average weight and weight variation, friability, thickness, hardness, disintegration time, subdivision of tablets, moisture content, dissolution of paracetamol, assay, uniformity of dosage units, related substances, residual solvents and microbial tests.
Release and end of shelf-life specification are identical except for hardness.
The analytical methods have been adequately described and validated. The validation of the methods for assay and related substances showed that the methods are stability indicating. Batch analysis data of three pilot-scale batches have been provided, demonstrating compliance with the release specification.

Container closure system
Specifications and test methods for all packaging components are provided. The following proposed packaging is acceptable:

- Bottle pack (100 pieces), 200 ml HDPE bottle with 38 mm child-resistant closure
- Blister pack (10 strips x 10 pieces), clear, transparent PVC film and plain aluminium foil
- Bulk pack (100 pieces) in LDPE bag

The bulk pack materials comply with the Ph.Eur. monograph on immediate packaging Materials Intended to be in direct contact with the active substance or medicinal product and the closure of the bottle pack complies with Directive 2002/72/EC. For the other two packagings reference is also made to the Ph.Eur. monographs.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60% 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 bulk and blister packaging.
The stability results show that the tablets are stable under both accelerated and long-term conditions under the proposed packaging conditions. No specific trends or patterns are noted for any of the parameters. Results from a photostability study show that the product is not sensitive to light.
Therefore, the approved shelf-life is 24 months packed in a PVC/Al-blister without special storage condition.

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

In order to obtain a biowaiver, an expert report was submitted to support this application. Reference is made to the *Note for Guidance on the investigation of bioavailability and bioequivalence.*

Active substance
Pharmacokinetics
For paracetamol there are no indications that the type of oral dosage form affects the bioavailability. Similar values have been found for the bioavailability of solid oral dosage forms (tablets) and liquid oral dosage forms (effervescent tablets).
Absorption as well as biotransformation is independent of the administered dose in the therapeutic range (250-1000 mg). Although paracetamol shows a considerable first-pass effect (30-40%), it has been demonstrated that the absorption of paracetamol is complete. Moreover, reported bioequivalence between orally administered aqueous and solid formulations of paracetamol is supportive, as it indicates that there are very little absorption limitations of a paracetamol formulation as long as it can be demonstrated that it disintegrates and dissolves rapidly.

Biopharmaceutical classification system (BCS)
It is debated whether a biowaiver would be valid, as only drugs of BCS Class I can be candidates for biowaiver. Classification System biowaiver is applicable.
Paracetamol is very soluble and almost 100% absorbed from the GI tract and it appears to have a wide therapeutic window. Hence, it may be inferred that paracetamol is not a narrow therapeutic index drug (NTID) and is therefore eligible for a BCS-based biowaiver.
BCS-based biowaivers are applicable for a drug product if the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I) or high solubility and limited absorption (BCS class III). Since paracetamol is highly soluble and its absorption is complete, it is appropriate to classify it as a BCS class I compound.

Medicinal product
In vitro dissolution
Paracetamol PharmaMatch 1000 mg tablets and Panadol 1000 mg Artrose tablets release more than 85% of the paracetamol within 15 minutes in all dissolution media. The requirement of 85% release within 15 minutes is easily met and therefore the similarity of dissolution profiles is accepted as demonstrated (see quality part of the report).

Excipients
Only well-established excipients are used in usual amounts. Furthermore, considering the amounts in which they are used, none of the excipients can be classified as 'active' excipients. Hence, it may be concluded that the bioavailability of paracetamol, a BCS class I compound, is not affected by the excipients.

Conclusion
The application contains an adequate review of published clinical data. It can be concluded that the requirements for a biowaiver as mentioned in the NfG on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and in the draft of the revision of this guideline are met for Paracetamol PharmaMatch 1000 mg.

Paracetamol is a long-standing drug and its safety/efficacy profile and use are well established. A biowaiver has been granted.

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 national procedure is in accordance with that accepted for the reference product Panadol 1000 mg Artrose.

Readability test

The package leaflet has not been evaluated via a user consultation study. This is considered to be acceptable since the package leaflet of an already approved paracetamol product, used as a reference for the product texts, have been tested and approved.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol PharmaMatch 1000 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Panadol 1000 mg Artrose tablets. Panadol Artrose is a well-known medicinal product with an established favourable efficacy and safety profile.

No comparative bioavailability or bioequivalence study was carried out. Instead, reference was made to fulfilling all requirements for a biowaiver. This has been sufficiently demonstrated.

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. 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. Paracetamol PharmaMatch 1000 mg, tablets was authorised in the Netherlands on 10 November 2010.

There were no post-approval commitments made during the procedure.

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
Change in the name and/or address of the MAH.	--	IA	22-12-2010	21-1-2011	Approval	N
Extension of shelf-life to 36 months.	--	IB	18-5-2011	22-6-211	Approval	N
Addtion of a 200 mL HDPE bottle as package.	--	IB	18-5-2011	22-6-211	Approval	N