CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Paracetamol Sandoz 500 mg and 1000 mg, tablets
Sandoz 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/2729/001-002/MR
Registration number in the Netherlands: RVG 111619-111620

15 May 2013

Pharmacotherapeutic group:	other analgesics and antipyretics
ATC code:	N02BE01
Route of administration:	oral
Therapeutic indication:	mild to moderate pain and fever (500 mg); mild to moderate pain associated with osteoarthritis of the hip and knee (1000 mg)
Prescription status:	non prescription (500 mg), prescription only (1000 mg)
Date of first authorisation in NL:	17 April 2012
Concerned Member States:	Mutual recognition procedure with BE, DK, FI, IT, LU, RO; 500 mg only - AT, HU; 1000 mg only - PL
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 member states have granted a marketing authorisation for Paracetamol Sandoz 500 mg and 1000 mg, tablets from Sandoz B.V. The date of authorisation was on 17 April 2012 in the Netherlands.

Paracetamol Sandoz 500 mg is indicated for mild to moderate pain and fever
Paracetamol Sandoz 1000 mg is indicated for mild to moderate pain associated with osteoarthritis of the hip and knee.

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

Paracetamol has analgesic and antipyretic actions, but it has no anti-inflammatory properties. The mechanism of action of paracetamol has not been fully clarified. The effect seems to be based on inhibition of the enzyme prostaglandin synthetase, but this does not explain the lack of anti-inflammatory actions. Distribution of paracetamol throughout the body and thus the location of the inhibition of prostaglandin synthetase may also be of importance. The benefit of paracetamol lies in the fact that some of the adverse effects characteristic of NSAIDs are completely or largely absent.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Panadol 500 mg and Panadol 1000 mg Artrose tablets (NL License RVG 18550, 26161) which have been registered in the Netherlands by GlaxoSmithKline Healthcare B.V. since 24 July 1995 and 11 December 2000, respectively. In addition, reference is made to Panadol 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.
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 this product 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.*). It is a white crystalline powder, which is sparingly soluble in water. 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 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 additional requirements for sieve analysis and bulk density. 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 Sandoz 500 mg is a white, caplet-shaped tablet debossed “500” on one side and plain on the other side.
Paracetamol Sandoz 1000 mg is a white to off-white, caplet-shaped tablet debossed with scoreline between “10” and “00” on one side and scoreline between “PA” and “RA” on the other side. The tablet can be divided into equal doses.

The tablets are packed in PVC/aluminium blister packs and in PE bottles (100 tablets).

The excipients are: povidone K-30 (E1291), pre-gelatinized starch, sodium starch glycolate, stearic acid (E570).

The two tablet strengths are dose proportional.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Since paracetamol is eligible for a biowaiver, no bioequivalence study was performed. Comparative dissolution profiles have been included. The drug release was found to be over 85% after 15 min. for all batches and all dissolution media. Subdivision of tablets is part of the product specifications and according to European guidelines. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of two steps: wet granulation followed by compression. The manufacturing process is a standard process and has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for five full-scale batches and three pilot-scale batches of 500 mg tablets and two full-scale batches of 1000 mg tablets. The product is manufactured using conventional manufacturing techniques.

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 HPLC methods for assay and related substances showed that the methods are stability indicating. Batch analyses data of three pilot-scale batches have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two batches of 500 mg tablets and three batches of 1000 mg tablets stored at 25°C/60% RH (24/36 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 at accelerated and long-term stability conditions under the proposed packaging conditions. No specific trends or patterns are noted for any of the parameters.
Results from a photostability study demonstrate that the product is not photosensitive. Therefore, the proposed shelf-life of 36 months packed in a PVC/Al-blister or HDPE bottle without special storage condition has been granted.
The results of an in-use study show that the product is stable after 90 days of open storage. It can therefore be inferred that opening the container multiple times will not influence the stability of the tablets negatively. A storage claim after first opening is not required.

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 Panadol, 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 member states 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 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.
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.

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

Paracetamol is a long-standing drug and its safety/efficacy profile and use are well established.
Since Paracetamol Sandoz 500 mg and 1000 mg tablets are immediate release, solid pharmaceutical forms for oral administration and systemic action, the concept of the Biopharmaceutics Classification System biowaiver is applicable.

Paracetamol is a BCS Class I drug, *i.e*. highly permeable and highly soluble. The excipients used in the tablet formulation are in part comparable to the excipients used in the reference formulation. The other excipients are used in normal quantities and are considered not to affect bioavailability. Dissolution data at a pH 1.2, 4.5 and 6.8 between test and reference showed comparable dissolution, *i.e.* more than 85% within 15 min. In addition, paracetamol is not considered a narrow therapeutic index drug. Hence, a biowaiver has been granted.

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 post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product. The MAH committed to resolve any outstanding pharmacovigilance issues within 3 months after finalization of the MRP. This includes having a database which is validated with appropriate security and quality controls.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with those accepted for other European procedures. This is acceptable.

Readability test
The package leaflet has not been evaluated via a user consultation study. Bridging is proposed to the PL of an already approved paracetamol product.
The proposed PL and the tested PL have a common design. The outcome of the user testing referred to shows that the tested population could find information about indication and posology and could also understand the information. Bridging to the proposed PL is considered acceptable; separate use testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol Sandoz 500 mg and 1000 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Panadol 500 mg and Panadol 1000 mg Artrose tablets. Panadol is a well-known medicinal product with an established favourable efficacy and safety profile. In the Netherlands, the prescription status for the 1000 mg formulation is prescription only. The 500 mg formulation is a non-prescription product.

No comparative bioavailability or bioequivalence study was carried out. Instead, reference was made to fulfilling all requirements for a biowaiver as paracetamol is a BCS Class I drug. 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. Paracetamol Sandoz 500 mg and 1000 mg, tablets were authorised in the Netherlands on 17 April 2012.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 15 February 2013.

The date for the first renewal will be: 12 April 2017.

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