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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Demneg 500 mg tablets
Genmed 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/2788/001/DC
Registration number in the Netherlands: RVG 112345

11 September 2014

Pharmacotherapeutic group:	other analgesics and antipyretics
ATC code:	N02BE01
Route of administration:	oral
Therapeutic indication:	Symptomatic treatment of mild to moderate pain and/or fever.
Prescription status:	no prescription
Date of authorisation in NL:	28 July 2014
Concerned Member States:	Decentralised procedure with CZ, EE, LT, LV, PL and SK
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 Demneg 500 mg tablets, from Genmed B.V. The date of authorisation was on 28 July 2014 in the Netherlands.

The product is indicated for the symptomatic treatment of mild to moderate pain and/or fever.

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

Paracetamol is an effective antipyretic and analgesic agent. However, it has no antiinflammatory effect. The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy without a conspicuous peripheral anti-inflammatory activity.

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 decentralised procedure concerns a generic application claiming essential similarity with the innovator product Panadol Zapp 500 mg tablet (NL License RVG 26469) which has been registered in The Netherlands by GlaxoSmithKline Healthcare since 05 August 2002 (original product). 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 a request for a biowaiver was submitted. 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 (Ph.Eur.*). The drug substance is a white crystalline powder that is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
Stability data on the active substance have been provided, based on which a retest period of 5 years could be granted. As paracetamol is known to be photosensitive, the drug substance should be protected from light.

** 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
Demneg 500 mg is a white, biconvex, round tablet having dimension of 12.70 mm x 5.35 mm.

The tablets are packed in PVC/Aluminium blisters.

The excipients are: povidone K-29/32 (E1201), microcrystalline cellulose (E460), maize starch, stearic acid (E570).

Pharmaceutical development
The formulation development of the product has been described, the choice of excipients is justified and their functions explained. For the manufacturing of the tablets, a wet granulation process was selected. Information and dissolution data at various pH values on the reference batch and test batch used in the bioequivalence study have been presented. The packaging is common for this kind of dosage form.

Information on the pharmaceutical development of the product has not been provided. However, in view of the history of the product, Paracetamol Genmed was registered on the Turkish market under the trade name Parol by the approval of Turkish Ministry of Health in 1973, no objection was made.

Manufacturing process
The tablets are manufactured in a wet granulation process. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for three batches of commercial batch size.

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

Quality control of drug product
The product specification includes tests for description, average weight, disintegration time, friability, identification, dimensions, uniformity of dosage units, related substances, assay, dissolution and microbial contamination. The shelf-life specification is identical to the release specification.
For the analytical methods BP methods from the monograph on paracetamol tablets have been adopted. Batch analytical data from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for seven batches of commercial batch size stored at 25°C/60%RH and 40°C/75%RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/Al blisters in a carton box.
On the basis of the submitted data a shelf-life of 5 years could be granted, with the storage condition 'keep blister in the outer carton in order to protect from light'.

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 Zapp 500 mg tablet, 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

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.

Biowaiver
A claim for biowaiver was requested on the following grounds presented by the MAH:

- According to the Biopharmaceutical Classification System (BCS), paracetamol belongs to Class III i.e. highly soluble and low permeable, although possessing properties borderline to BCS class I (Kalantzi et al., 2006).
- Solubility: paracetamol is not substantially ionized at pH less than 9 and, therefore, its solubility does not vary with pH. A dose of 500 mg is soluble in 21 ml, so far below the cut-off limit for an API to be "highly soluble" as defined by the BCS Guidance (i.e. 250 ml or less of aqueous media over the pH range of 1 – 7.5).
- Permeability: the fraction of dose absorbed in humans is higher than 80%. The cut-off limit for an API to be "highly permeable" as defined by the BCS Guidance is higher than 90%. On the basis of this paracetamol is BCS class III, which enables a BCS biowaiver given that dissolution is very rapid and excipients will not affect the absorption.
- The test product Paracetamol 500 mg tablets is a very rapidly dissolving IR solid oral dosage form, i.e. no less than 85% of the labelled amount of the drug substance dissolves within 15 minutes.

According the MEB several studies presented in the literature have shown that paracetamol has a high absolute bioavailability. Urinary recovery showed almost complete recovery of paracetamol and its metabolites. The latter were not formed in the intestine, but after absorption. Sufficient proof is available showing that bioavailability of paracetamol after oral administration is more than 85%. Therefore the MEB considered paracetamol in fact to be a BCS class I substance (limited absorption, highly dissolvable) and is therefore an acceptable candidate for a BCS biowaiver. Paracetamol has also a wide therapeutic range, with reported low risk of bio-inequivalence for regular IR tablets.

The dissolution testing has been performed with an appropriate method, using 12 tablets.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver is accepted.

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 that accepted for another paracetamol generics.

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 two rounds with 10 participants each. Thirteen questions were asked. In the first round the patient leaflet of Paracetamol Genmed 500 mg tablets scored 100% on the traceability criterion for each question, except question 3 (90%). In the second round the score was 100%, except for question 10 (90%).
For each question the score for the comprehensibility and applicability criterion was higher than 80% in the first round and 90% or higher in the second round. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Demneg 500 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Panadol. Paracetamol has been in clinical use for more than 30 years, and is an active substance with recognised efficacy and an acceptable level of safety.

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.

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 <product> with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 May 2013. Demneg 500 mg tablets is authorised in the Netherlands on 28 July 2014.

The date for the first renewal will be: 29 May 2018.

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