

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Paracetamol Mylan 1000 mg, tablets
Mylan 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 105822

12 November 2012

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:	6 September 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 Mylan 1000 mg, tablets from Mylan B.V. The date of authorisation was on 6 September 2010 in the Netherlands.

The product is indicated for mild to moderate pain associated with arthrosis of the hip or knee.

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.*). It is a white crystalline powder, which is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. No polymorphs are reported in literature for paracetamol.

The CEP procedure is used for all three suppliers of 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

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

Reference to the CEP is made concerning the drug substance specifications. The specification of the MAH is in line with the specification of the Ph.Eur. and CEP holders. As compendial analytical methods are used, submission of validation data is not required. Batch analyses of the active substance manufacturers have been reviewed in relation to the approval of the Certificates of Suitability. Batch analysis results of the MAH are not required.

Stability of drug substance

The active substance sourced from the first CEP holder is stable for five years if stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The active substance sourced from the second active substance manufacturer is stable for five years if stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The active substance sourced from the third CEP holder is stable for two years if stored under the conditions specified.

** 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 Mylan 1000 mg is a white to off white biconvex oblong, uncoated tablet with a break line on both sides. The tablet can be divided into equal halves.

The tablets are packed in PVC-Al blisters.

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

Pharmaceutical development

The description of the formulation comprises the final proposed formulation. Comparative dissolution profiles demonstrate that paracetamol 1000 mg tablets release more than 85% of the paracetamol within 10 minutes in all dissolution media. Testing was done versus the UK reference product. The MAH has justified the use of the UK reference product and has provided comparative dissolution profiles with the reference product sourced from the Netherlands.

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

A standard manufacturing process based on wet granulation is applied. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorization.

Control of excipients

All excipients used are controlled according to the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for fill in appearance, identity, assay, degradation, disintegration, dissolution, hardness, water content, friability, uniformity of dosage units, average weight, microbial purity and subdivision of tablets. The proposed specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided three pilot-scale batches stored at 25°C/60% RH (24 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 the packaging proposed for marketing. No significant trends are seen and all results comply with the limits in the finished product specifications. Based on the 24 months stability data a shelf life of 36 months can be granted. As paracetamol is weakly photosensitive, the storage condition 'keep blister in the outer carton' is employed.

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 Board 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 Board agreed that no further clinical studies are required.

Biowaiver

The MAH discussed the criteria for biowaiver according Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98).

Active substance

Therapeutic index margin of the active substance

The MAH stated that the non-critical therapeutic range of paracetamol is demonstrated by the fact that paracetamol is not a narrow therapeutic index drug (NTID).

The different dosing regimens are addressed for all age groups of patients and the high first-pass effect of paracetamol and the hepatotoxicity. The MAH concludes that with respect to the non-critical therapeutic range of paracetamol, large variations in the first-pass metabolism lead to differences in the serum concentrations of paracetamol. Moreover, these serum levels are not clearly correlated to the analgesic effect.

Furthermore, paracetamol appears to have a very wide therapeutic window. The difference between the maximum daily dose (4 g) and the minimal toxic dose (10 g) is at least a factor of 2.5, in adults. In children, the difference is even larger; the maximum daily dose is 50 mg/kg, compared to a minimal toxic dose of 150 mg/kg. Therefore, it may be inferred that paracetamol is not a narrow therapeutic index drug (NTID) and there is little risk of therapeutic failure or adverse drug reactions and no requirement for special precautions with respect to precision and accuracy of dosing.

Pharmacokinetic properties

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.

Solubility

When an active substance is highly soluble, the product could be in general exempted from bioequivalence studies, unless, considering the other characteristics, the exemption could entail a potential risk. Polymorphism and particle size are major determinants of dissolution rate and special attention should be paid to these characteristics. An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate release product is dissolved in 250 ml of each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, and 6.8). For paracetamol granules this is 1 g in 250 ml, which corresponds to 4 mg/ml.

The MAH submitted many literature references in which the solubility at different temperatures is discussed. The argumentation that paracetamol can be considered as a highly soluble compound is accepted.

Biopharmaceutical classification system (BCS)

According to the BCS, drugs can be divided into four major categories based on their solubility and permeability. Drugs, which show good solubility and permeability, are indexed into class I. These drugs are generally suitable for a biowaiver. Class II contains compounds, which exhibit poor solubility but good permeability. These drugs are in general not appropriate for a biowaiver.

On the other hand, drugs in class III display good solubility and poor permeability. Whether a biowaiver is suitable for drugs in this category, is still subject of discussion. Finally, class IV contains drugs which exhibit poor solubility as well as poor permeability. As a rule, a biowaiver is not appropriate for these drugs. It has been suggested that biowaivers should be extended to BCS class III drugs that exhibit rapid dissolution, since there are equally compelling reasons to grant biowaivers to class III drugs as there are for class I drugs. The absorption of a class III drug is likely limited by its permeability and less dependent

upon its formulation, and its bioavailability may be determined by its *in vivo* permeability pattern. If the dissolution of class III products is rapid under all physiological pH conditions, it can be expected that they will behave like an oral solution *in vivo*.

Initially, paracetamol was classified as a BCS class III compound, however, recently a technical report from the WHO expert committee on specifications for pharmaceutical preparations, classifies it as a BCS class I compound, since it is highly soluble and permeable. Other sources also classify paracetamol as a class I compound. The high permeability is derived from the high bioavailability (88%) of this drug. When a drug substance is absorbed to an extent of 90% or more, it is considered highly permeable by FDA guidance. This permeability criterion was relaxed to not less than 85% by WHO guidance and the CPMP draft guidance. 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

In case of exemption from bioequivalence studies, *in vitro* data should demonstrate the similarity of dissolution profile between the test product and the reference product in each of three buffers within the range of pH 1-8 at 37°C (preferably at or about 1.0, 4.6, 6.8). However, in cases where more than 85% of the active substance are dissolved within 15 minutes, the similarity of dissolution profiles may be accepted as demonstrated. If an active substance is considered highly water soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH-interval expected after product administration. A bioequivalence study may in those situations be waived based on case history and similarity in dissolution profiles which are based on discriminatory testing, provided that the other exemption criteria are met.

The similarity should be justified by dissolution profiles, covering at least three time points, attained at three different buffers (normally pH range 1-6.8; in cases where it is considered necessary pH range 1-8). In case of a drug or excipients that are insensitive to pH, profiles from only two buffer systems are required.

The dissolution of paracetamol from tablets (n = 12) of Paracetamol Mylan 1000 mg tablets has been studied at different pH values. Panadol® Tablets 1g, marketed by GSK in the UK, has been used as reference product for comparative reasons.

Both Paracetamol Mylan 1000 mg and Panadol Tablets 1 g tablets release more than 85% of the paracetamol within 10 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.

Excipients

The excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. No atypically large amounts of known excipients or new excipients are used, so no additional documentation is required.

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 Mylan 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 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 was performed on the leaflet for the French product Paracétamol Qualimed 500 mg, comprimé.

A questionnaire of 11 questions was created. After a preliminary round with 2 participants, two test rounds were performed with the mock up version of the PIL with 10 participants in each round. This led to the following main results: at least 90% of the participants were able to find the correct information and at least 90% of the participants were able to answer the questions correctly in the first round. In the second round these percentages were 100%. It can be concluded that the readability of the tested PIL is of an acceptable level.

The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. There were no revisions made to the PIL before, during and after the testing.

A bridging study was performed to bridge the French equivalent of Paracetamol Mylan 1000 mg with the tested product. Although the target population of Paracetamol Mylan 1000 mg (children over 50 kg) is different from the tested product (children over 27 kg), the tested population consisted of adults. Therewith the difference in target population does not have impact on the suitability for bridging. Nine out of eleven questions of the readability test can be used for the PIL of Paracetamol Mylan 1000 mg. Herewith key safety issues are sufficiently covered. The layouts of the PILs are different, but not substantial. The content of both PILs is nearly similar.

The bridging study shows that the PILs of Paracétamol Qualimed 500 mg, comprimé and Paracetamol Mylan 1000 mg are highly similar. No separate user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol Mylan 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 Mylan 1000 mg, tablets was authorised in the Netherlands on 6 September 2010.

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

Quality - medicinal product

- The MAH committed to submit the end results of the stability studies on the drug product over the full shelf-life period. This commitment has been fulfilled.

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
Change in pack size of the finished product; introduction of a 50 tablet pack for hospital use only.	--	IB	1-2-2011	10-2-2011	Approval	No
Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions; tightening of m-process limits; tightening of specification limits; minor changes to an approved test procedure.	--	IA/G	4-4-2011	3-6-2011	Approval	No
Post-approval commitment: End results of the stability studies on the drug product over the full shelf-life period.	--	PAC	10-5-2011	14-6-2011	Approval	No
Change in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/ hybrid/biosimilar medicinal products following assessment of the same change for the reference product.	--	IB	7-3-2012	19-3-2012	Approval	No
Replacement or addition of a site where batch control/testing takes place.	--	IA	7-3-2012	6-5-2012	Approval	No