CBG MEB

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

# Paracetamol Smelt Actavis 250 mg and 500 mg, orodispersible tablets Actavis Group PTC ehf, Iceland

# 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/1541/001-002/DC**
**Registration number in the Netherlands: RVG 103414, 103421**

**11 August 2010**

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|---|---|
| Pharmacotherapeutic group: | other analgesics and antipyretics: anilides |
| ATC code: | N02BE01 |
| Route of administration: | oral |
| Therapeutic indication: | Symptomatic treatment of mild to moderate pain and/or fever - 250 mg: in children ≥ 4 years and adolescents only. 500 mg: in adults and adolescents only. |
| Prescription status: | non prescription |
| Date of authorisation in NL: | 2 August 2010 |
| Concerned Member States: | Decentralised procedure with DK, FI, FR, IS, IT, NO, RO; 500 mg only - EE, LT, LV |
| Application type/legal basis: | Directive 2001/83/EC, Article 10(3) |

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 Smelt Actavis 250 mg and 500 mg, orodispersible tablets from Actavis Group PTC ehf. The date of authorisation was on 2 August 2010 the Netherlands.

The product is indicated for symptomatic treatment of mild to moderate pain and/or fever in children from the age of four and adolescents only.
The 500 mg product is indicated for symptomatic treatment of mild to moderate pain and/or fever in adults and adolescents only.
The maximum daily dose according to the SPC is 3000 mg in adults.

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 hybrid application with a change in pharmaceutical form. Paracetamol Smelt Actavis 250 mg and 500 mg are orodispersible tablets, whereas the reference product Panadol 500 mg is an immediate release tablet. Furthermore, the 250 mg tablet is a different strength. Oral paracetamol has been marketed in Europe for more than 50 years, mostly as conventional immediate release tablets containing 500 mg paracetamol. In the Netherlands, Panadol Gladde Tablet 500 mg, tablets has been registered by GlaxoSmithKline Consumer Healthcare B.V. since 1995 (NL License RVG 18550). The product was first authorised in NL in 1956. In addition, reference is made to Panadol authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) 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 a bioequivalence study in which the pharmacokinetic profile of the 500 mg product is compared with the pharmacokinetic profile of the reference product Panadol 500 mg film-coated tablets, registered in the Netherlands. 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. These products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

Scientific advice by the MEB was given on 27 June 2006 and 9 November 2006 on quality and bioequivalence requirements, obtaining a biowaiver and the choice of reference product Panadol.

No paediatric development programme has been submitted, as this is not required for substitutional 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 these product types 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.

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. and the CEP, with additional requirements for particle size. The specification is acceptable in view of various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 30°/65% RH (3 years) and 40°C/75 RH (6 months). The batches were adequately stored. In addition data of batches stored at ambient warehouse conditions up to 5 years are provided. No out of specification or significant change is seen. The active substance is stable for 5 years when stored under the proposed conditions.

** 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 Smelt Actavis 250 mg and 500 mg are white to off-white round, flat face radius edge tablets.

The orodispersible tablets are packed in PVC/PVdC or Aclar®/PVC blister with printed peelable foil/paper backing.

The excipients are: ethylcellulose, mannitol (E421), microcrystalline cellulose (E460), crospovidone, aspartame (E951), magnesium stearate (E572), strawberry flavour (contains amongst other lactose, maltodextrine, arabic gum (E414)).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The objective was to develop a very rapid dissolution profile with acceptable organoleptic characteristics; this was achieved by developing microencapsulated paracetamol.
The Dutch reference Panadol 500 mg tablets was adopted as the reference product for in-vitro dissolution studies and the bioequivalence study. The compositions of Panadol tablets 500 mg in the countries where the information is available are equivalent or at least functionally equivalent.
Comparative multi speed and multimedia dissolution profiles have been generated on a clinical batch of Paracetamol Smelt Actavis 500 mg, the reference product Panadol 500 mg tablets, a Paracetamol 250 mg orodispersible tablets batch and half Panadol tablets. Data showed that more than 85% dissolved in 15 min for all tested tablet formulations.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing consists of four production steps: microencapsulation of paracetamol, mannitol granulation, blending of microcapsules, mannitol granulation, excipients and tabletting, packaging.
The manufacturing process has not yet been adequately validated according to relevant European guidelines. Process validation data are not yet provided at a production scale; these will be provided post-approval.

Control of excipients
The excipients comply with the Ph.Eur. and adequate in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, moisture, disintegration, dissolution, degradation, uniformity of dosage units and microbial purity. Shelf-life requirements are widened for moisture. 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 of each strength, demonstrating compliance with the release specification. The MAH committed to provide batch analysis results of the first three commercial-scale batches for both product strengths.

Stability of drug product
Stability data on the product have been provided two pilot scaled batches of each strength stored at 25°C/60% RH (24 months) AND 40°C/75% RH (6 months). Stability data on bulk tablets in a bulk container have been provided of 1 batch of each strength stored at 15-30°C (3 and 6 months). The conditions used for the commercial packaging in the stability studies are according to the ICH stability guideline. The results do not show out of specification or significant trends. A shelf-life of 24 months with no special storage conditions could be granted. The MAH committed to perform stability studies under ICH conditions on bulk tablets of the first three industrial-scale validation batches.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose as part of the strawberry flavour is the only possible substance of ruminant animal origin. A declaration of conformity with directive 92/46/EEC was provided.

## 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

Paracetamol is a well-known active substance with established efficacy and tolerability.

For this hybrid application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Paracetamol Smelt Actavis 500 mg, orodispersible tablets (Actavis Group PTC ehf, Iceland) is compared with the pharmacokinetic profile of the reference product Panadol 500 mg film-coated tablets (GlaxoSmithKline B.V., the Netherlands).

*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 in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Design*
A three-way, single dose, balanced, randomised, cross-over bioequivalence study was carried out according to a Latin square design. The study was carried out under fasted conditions in 27 non-smoking, healthy subjects (males and females). Fasting was continued until 4 hours after administration.
The objective of a study was to assess the bioequivalence of a test formulation Paracetamol Smelt Actavis 500 mg orodispersible tablets administered with (T1) or without water (T2) compared to the reference Panadol 500 mg film-coated tablets administered at a single dose of 500 mg with water.
Under test condition T1, tablets were swallowed as a whole with 240 ml water. Under test condition T2, subjects were instructed to place the tablet on the upper surface of their tongue and gently move it around within their mouth until it fully disintegrated (about 60 seconds) forming a suspension, swallowing the suspension as if they would do normally when taking food. No water was taken under condition T2. The Clinical Investigator checked the drug ingestion by a mouth inspection in all study arms.
The three single-treatment sessions were separated by wash out periods between 4-7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

*Analytical/statistical methods*
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.

*Results*
Two randomised subjects did not show up before the first dose and one subject dropped out for personal reasons. Twenty-four subjects completed the study and were eligible for pharmacokinetic analysis.

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

| **Treatment N=24** | **$AUC_{0-t}$** µg.h/ml | **$AUC_{0-\infty}$** µg.h/ml | **$C_{max}$** µg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test (T1)** | 22.44 | 22.43 | 7.24 | 0.66 | 3.82 |
| **Test (T2)** | 21.00 | 21.69 | 7.64 | 0.84 | 3.28 |
| **Reference** | 20.77 | 21.72 | 7.32 | 0.85 | 3.68 |
| ***Ratio T1/R** | 1.03 | 1.03 | 1.01 | - | - |

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|---|---|---|---|---|---|
| **(90% CI)** | (0.996-1.062) | (0.994-1.063) | (0.909-1.103) | | |
| ***Ratio T2/R (90% CI)** | 1.01 (0.981-1.045) | 1.00 (0.968-1.036) | 1.04 (0.940-1.140) | - | - |
| **CV (%)** | - | - | - | - | - |
| **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity<br>**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration<br>**$t_{1/2}$** 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 Smelt Actavis 500 mg, orodispersible tablets and Panadol 500 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption in both conditions of use, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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.

*Extrapolation to 250 mg strength*
The 250 mg strength is not included in the bioequivalence study. The results and conclusion of the bioequivalence study with the 500 mg formulation can be extrapolated, as the following conditions are met:
- similar manufacturer;
- dose proportional qualitative composition;
- the tablets of the two different strengths are dose-linear in composition;
- dissolution profiles of test and reference product (500 mg whole or half tablet) are similar (> 85% dissolved within 15 minutes);
- linear kinetics of paracetamol.

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
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 SPC for was brought in line with the SPCs for procedures NL/H/1330/001-002/DC and UK/H/1253/001/DC, concerning other paracetamol products.

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 a pilot test with 3 participants, followed by two rounds with 10 participants each. A total of nineteen questions were asked; seventeen questions addressed key safety messages within the package leaflet.

The leaflet passed the defined success criteria: 90% of the test participants are able to find the information requested within the package leaflet of which 90% can show that they understand it.

Therefore the test was deemed to be successful and no updates are necessary to the package leaflet. A number of general questions relating to the design and layout of the PIL were included in the interview. It was generally perceived that the design/layout was easy to follow.

The readability test has been sufficiently performed.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Paracetamol Smelt Actavis 250 mg and 500 mg, orodispersible tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Panadol 500 mg film-coated tablets. Panadol is a well-known medicinal product with an established favourable efficacy and safety profile.

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 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 Paracetamol Smelt Actavis 250 mg and 500 mg, orodispersible tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 February 2010. Paracetamol Smelt Actavis 250 mg and 500 mg, orodispersible tablets were authorised in the Netherlands on 2 August 2010.

A European harmonised birth date has been allocated and subsequently the first data lock point for paracetamol is May 2012. The first PSUR will cover the period from February 2010 to May 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: January 2013.

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

Quality - medicinal product

- The MAH committed to provide process validation data on microencapsulation according to the process validation scheme provided before marketing the product.
- The MAH committed to provide batch analysis results of the first three commercial-scale batches for both product strengths.
- The MAH committed to support the existing bulk holding stability data; stability studies under ICH conditions on bulk tablets will be started on the first three industrial-scale validation batches.

## 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 test procedure for an excipient; other changes to a test procedure (including replacement or addition). | NL/H/1541/ 001-002/IB/ 001 | IB | 17-6-2010 | 17-7-2010 | Approval | N |
| Changes in components of the flavouring or colouring system; addition, deletion or replacement. | NL/H/1541/ 001-002/IA/ 002 | IA | 22-6-2010 | 22-6-2010 | Non approval | N |