LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Paracetamol EQL Pharma
# (paracetamol)

# Asp no: 2017-0200, 2017-0201

**This module reflects the scientific discussion for the approval of Paracetamol EQL Pharma. The procedure was finalised on 2018-02-26. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

# I. INTRODUCTION

EQL Pharma AB has applied for a marketing authorisation for Paracetamol EQL Pharma, 500 mg and 1 g, tablet. The active substance is paracetamol.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

## III.1 Discussion on the non-clinical aspects

Since paracetamol has been used clinically for a very long time there is an extensive clinical experience with paracetamol that largely supersedes non-clinical data. No further non-clinical data have been submitted or are considered necessary. A non-clinical overview, based on submitted publications included in the dossier, is considered to be adequate.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

The submitted literature overview describing the clinical pharmacokinetics was limited considering what is normally required of a well-established use application; however the data provided is considered sufficient as the pharmacokinetics of paracetamol is well understood.

No bioequivalence study was submitted since a BCS biowaiver was applied for. An approved biowaiver is a requirement to ensure that the cited literature data is relevant also for the proposed new product. Paracetamol fulfils the requirements being a highly soluble compound (paracetamol is considered to be a BCS class I compound) and not being a narrow therapeutic index medical product. There are differences in the composition of the applied product and the innovator product compared to. However, considering the drug substance being BCS class I, the differences are considered acceptable since it is not considered likely that these differences would affect bioavailability. In vitro dissolution data comparing the applied product with the innovator product was provided. Thus a BCS biowaiver is acceptable.

## IV.2 Pharmacodynamics

While treatment with paracetamol is well established, its mode of action underlying its analgesic and antipyretic effect is not fully understood. Paracetamol is only a weak inhibitor of cyclo-oxygenase-1 and -2, which are important for the prostaglandin synthesis. In has been suggested that central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this may explain why paracetamol has an antipyretic and analgesic effect without a conspicuous peripheral anti-inflammatory activity.

## IV.3 Clinical efficacy

Although the submitted review was considered meagre considering what is normally required of a well-established use application, the data provided are considered sufficient to support that paracetamol is widely established in the treatment of mild-moderate pain and fever and for the claimed indications.

## IV.4 Clinical safety

In general, paracetamol is well tolerated at therapeutic dose levels. In contrast to NSAIDs, gastric intolerability and bleeding disorders do practically not occur at regular use of paracetamol. Asthmatic reactions may occur in patients with a history of asthma, but significantly less than NSAIDs. Rare cases of nephropathy and severe dermal reactions, e.g.

Steven-Johnsons syndrome, have been reported. The main clinical risk of high doses of paracetamol is liver failure, due to the hepatotoxic effects of the paracetamol metabolite N-acetyl-para-benzoquinone imine. Since paracetamol is well-tolerated at normal use and the safety issues of paracetamol are well-known and widely documented, the meagre documentation can be considered just about acceptable.

## IV.5 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Paracetamol EQL Pharma.

Safety specification

Summary table of safety concerns

| | |
|---|---|
| Important identified risks | Hepatotoxicity in overdose<br>Severe skin reactions |
| Important potential risks | None |
| Missing information | None |

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

*The RMP is approvable.*

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# V. USER CONSULTATION

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 language used for the purpose of user testing the PL was Swedish.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Paracetamol EQL Pharma, 500 mg and 1 g, tablet is recommended for approval.

**List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

Paracetamol EQL Pharma, 500 mg and 1 g, tablet was approved in the national procedure on 2018-02-26.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se