LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

# Metformin EQL
# (metformin hydrochloride)

# Asp no: 2017-1288, 2017-1289

**This module reflects the scientific discussion for the approval of Metformin EQL. The procedure was finalised on 2018-11-01. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

The application for Metformin EQL, 500 mg and 850 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, EQL Pharma AB, applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Glucophage, 500 mg, tablet authorised in Germany since 1965, with Merck Serono GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Glucophage, 500 mg, tablet from Germany with Merck Serono GmbH as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 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 this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Metformin EQL with the reference product Glucophage.

Pharmacokinetic properties of the active substance
*Absorption:* The absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is 50-60%. Following an oral dose of 500 mg or 850 mg maximal plasma concentrations occur at approximately 2.5 hours.

Food decreases the extent and slightly delays the absorption of metformin. Concomitant food intake decreases the $C_{max}$ and AUC by 40 and 25 %, respectively and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

The SmPC of the reference product recommends administration during or after meals.

*Linearity:* The pharmacokinetics is non-linear with a less than proportional increase in AUC with increasing dose.

*Elimination:* The terminal half-life is 6.5 hours.

Study 226-13
*Methods*
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (34 completed), comparing Metformin EQL, 500 mg, film-coated tablet with Glucophage, 500 mg, film-coated tablet under fed conditions. Blood samples for concentration analyses were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of metformin were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-t}$ and $C_{max}$. The study was conducted between 19 August 2014 and 07 September 2014.

*Results*
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for metformin, n=34.**

| Treatment | $AUC_{0-t}$ ng*h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **6568.75 ± 1418.89** | **774.57 ± 191.78** | **3.50 (1.00-8.00)** |
| **Reference** | **7001.40 ± 1307.47** | **839.92 ± 197.64** | **3.50 (1.00-6.00)** |
| ***Ratio (90% CI)** | **93.36 (89.52-97.37)** | **91.91 (87.26-96.79)** | **-** |

**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum plasma concentration

**calculated based on ln-transformed data*

For $AUC_{0-t}$ and $C_{max}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

A biowaiver was sought for the additional strength of 850 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. Clinical trials with metformin have demonstrated decreased bioavailability at higher doses, suggesting saturable intestinal absorption.

For drugs with non-linear pharmacokinetics characterised by a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or a strength in the linear range), i.e. in this situation two bioequivalence studies are needed. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that the general biowaiver criteria described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength (or a strength in the linear range).

It is sufficient to study only the lower strength of 500 mg since the substance is highly soluble and the non-linearity is not caused by limited solubility but is most probably due to e.g. saturation of uptake transporters.

It should be noted that based on the submitted data it is not clear if the pharmacokinetics of metformin is non-linear in the interval relevant for strength biowaiver (500-850 mg), i.e. if the difference in dose adjusted AUC is more than 25 %. However, if pharmacokinetics in this range could be classified as linear according to the definition given in the bioequivalence

guideline, it would still be acceptable to study the lower strength since the substance is highly soluble.

The test and reference products do not contain any excipients like e.g. sorbitol or mannitol that may affect gastrointestinal motility or transport proteins.

Thus, absence of studies with the additional strength (850 mg) is acceptable from a pharmacokinetic point of view.

The results of study 226-13 with 500 mg formulation CAN be extrapolated to other strength 850 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev 1, section 4.1.6.

Based on the submitted bioequivalence study, Metformin EQL is considered bioequivalent with Glucophage.

## IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

## IV.3 Risk Management Plan

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 Metformin EQL.

Safety specification

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Lactic acidosis |
| 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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.2 signed 2018-05-30 is considered acceptable.

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 MPA;
- 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

User consultations with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Metformin EQL Pharma, Dnr 111:2008/102406 regarding content and Paracetamol EQL, Dnr 5.4.1-2017-18035 and 5.4.1-2017-18036 regarding lay-out. The bridging report submitted by the applicant has been found acceptable.

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

The quality of the generic product, Metformin EQL, is found adequate. There are no objections to approval of Metformin EQL, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

**List of recommendations not falling under Article 21a/22 of Directive 2001/83 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

Metformin EQL 500 mg and 850 mg, film-coated tablet was approved in the national procedure on 2018-11-01.

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# 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)

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