LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Metronidazol EQL Pharma (metronidazole)

Asp no: 2018-0526, 2018-0527

This module reflects the scientific discussion for the approval of Metronidazol EQL Pharma. The procedure was finalised on 2019-05-28. 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

The application for Metronidazol EQL Pharma, 200 mg and 400 mg, filmcoated 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 Flagyl, 200 mg and 400 mg, tablet, authorised in Sweden since 1963, with Sanofi AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Flagyl, 200 mg and 400 mg, tablet from Sweden with Sanofi AB 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/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 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 a fed state bioequivalence study comparing Metronidazol EQL Pharma with the reference product Flagyl from Sanofi AB.

Pharmacokinetic properties of the active substance

Following oral administration, metronidazole is absorbed with a maximal plasma concentration C_{max} occurring at approximately 1-3 hours (t_{max}), has a bioavailability of about 90 % and a terminal half-life of about 8 hours. Following oral doses, the pharmacokinetics has been reported to be linear up to 2000 mg.

There are no dosing restrictions with respect to food in the Summary of Product Characteristics (SmPC) of the originator on the Swedish market.

Bioequivalence study (16-031)
Methods
This was a single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Metronidazol EQL Pharma, 400 mg, filmcoated tablet with Flagyl, 400 mg, tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of metronidazole 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 13/06/2017 and 23/06/2017.

Results
The results from the pharmacokinetic and statistical analysis are presented in **Error! Not a valid bookmark self-reference.** below.

Table 1. Pharmacokinetic parameters under fed conditions (non-transformed values; arithmetic mean ± SD, t_{max} (median)) for metronidazole, n=26.

Treatment	AUC_{0-t} ug*h/ml	C_{max} ug/ml	t_{max} h
Test	**122.318 ± 25.543**	**8.738 ± 1.282**	**4.144 ± 1.473 (median 4.00)**
Reference	**120.786 ± 22.188**	**9.103 ± 1.407**	**3.288 ± 0.982 (median 3.25)**
***Ratio % (90% CI)**	**100.76 (98.58-102.98)**	**96.01 (92.40-99.75)**	**-**

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 200 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/). However, as there are no dosing restrictions with respect to food in the SmPC of the originator on the Swedish market, the bioequivalence study should be conducted under fasting conditions, according to the guideline (EMA Guideline on the investigation of bioequivalence, CHMP/QWP/EWP/1401/98 Rev. 1).

To further support bioequivalence under fasting conditions, the Applicant has provided a scientific discussion with regard to the applicability of a BCS based biowaiver of Metronidazole tablets according to the guideline (Guideline on the investigation of bioequivalence, CHMP/QWP/EWP/1401/98 Rev. 1). This discussion includes in vitro solubility, intestinal absorption, in vitro dissolution rate and excipients.

Metronidazol EQL Pharma can be concluded to be a BCS class 1 product as it fulfils all conditions for a biowaiver according to Guideline on the investigation of bioequivalence, CHMP/QWP/EWP/1401/98 Rev. 1. Thus, a bioequivalence study in the fasted state is not needed, i.e. it can be waived.

The analytical methods used are acceptable.

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 version 0.2 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 Metronidazol EQL Pharma tablets.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
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
According to the MAH, the safety information in the proposed product information is aligned to the reference medicinal product. Routine risk minimisation is thus suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 07 Dec 2018 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 an 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 PIL 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 quality of the generic product, Metronidazol EQL Pharma, is found adequate. There are no objections to approval of Metronidazol EQL Pharma, 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/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

Metronidazol EQL Pharma, 200 mg, 400 mg, filmcoated tablet was approved in the national procedure on 2019-05-28.

LÄKEMEDELSVERKET
SWEDISH 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