Public Assessment Report

Scientific discussion

Metformin "Actavis PTC" 500 mg, 750 mg and 1000 mg prolonged release tablets

(Metformin hydrochloride)

DK/H/2272/001-003/DC

24 February 2015

This module reflects the scientific discussion for the approval of Metformin "Actavis PTC". The procedure was finalised on 14 May 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Metformin "Actavis PTC" 500 mg, 750 mg and 1000 mg prolonged release tablets, from Actavis Group PTC ehf.

The product is indicated for treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Metformin prolonged release tablets may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.
A comprehensive description of the indications and posology is given in the SmPC.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

This decentralised procedure concerns an application for a "hybrid" of the reference product Glucophage 500 mg, 850 mg and 1000 mg film-coated tablets, which has been registered in Denmark by Merck Santé s.a.s, since 1961, but withdrawn by the MAH in 2010.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each 500 mg prolonged release tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base. The 500 mg prolonged release tablets are white to off-white, capsule shaped uncoated tablets, 16.50 mm in length, 8.20 mm in width and 6.70 mm in thickness, debossed with 'XR500' on one side and plain on other side.

Each 750 mg prolonged release tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base. The 750 mg prolonged release tablets are white to off-white, capsule shaped, uncoated tablets, 19.60 mm in length, 9.30 mm in width and 7.40 mm in thickness, debossed with 'XR 750' on one side and plain on other side

Each 1000 mg prolonged release tablet contains 1000 mg metformin hydrochloride corresponding to 780 mg metformin base. The 1000 mg prolonged release tablets are white to off-white, capsule shaped, uncoated tablets, 21.10 mm in length, 10.10 mm in width and 8.90 mm in thickness, debossed with 'XR 1000' on one side and plain on other side.

The tablets are packed in blister strips composed of aluminium foil and PVC in pack sizes of 14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180 and 600 tablets. However, not all pack sizes may be marketed.

The tablets contain: Magnesium stearate; Silica, colloidal anhydrous; Povidone K30 and Hypromellose.

The RMS 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.

II.2 Drug Substance

The active substance, metformin hydrochloride, is described in the European Pharmacopoeia. It is a white crystalline powder. It is freely soluble in water, slightly soluble in ethanol (98%), practically insoluble in acetone and in methylene chloride. Its melting range is 222-226°C.

INN name: Metformin hydrochloride
Chemical name: 1,1-Dimethylbiguanide hydrochloride
Molecular formula: $C_4H_{11}N_5$, HCl
Molecular weight: 165.63

The MAH sources the substance from an external supplier holding a certificate of suitability from EDQM.

The finished product manufacturer's drug substance specification is in accordance with the CEP and additional requirements are established for residual xylene, particle size and microbiological quality.

Based on the provided stability data for the drug substance, an appropriate re-test period has been set.

II.3 Medicinal Product

The drug product is prolonged release tablets to be marketed in PVC/Aluminium blister packs in strengths of 500 mg, 750 mg and 1000 mg metformin hydrochloride. The tablets are dose proportional and formulated using common excipients described in the European Pharmacopoeia. The development of the product has been satisfactorily described.

The manufacturing process is adequately described and has been satisfactorily validated at pilot scale.

The drug product specifications cover appropriate parameters for this dosage form. Satisfactory validations of the analytical methods have been presented. Batch analysis data are presented for the batches used in the process validation studies showing compliance with the proposed specifications.
Long term and accelerated stability data of all strength tablets in the proposed market packaging are provided and a shelf-life of 2 years with no special storage conditions is accepted.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of metformin are well known. As metformin is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers numerous publications up to year 2010. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Metformin "Actavis PTC" is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Metformin is a well-known active substance with established efficacy and tolerability. As metformin is a widely used, well-known active substance, the MAH has not provided additional studies (apart from the bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical overview report refers numerous publications up to year 2010. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

Bioequivalence studies
To support the application the MAH has submitted 3 bioequivalence studies (single-dose fasted and fed and 1 multiple dose study) with Glucophage SR 1000 mg prolonged release tablets, Merck Serono, from the UK market as the reference product and 1 bioequivalence study (single dose fasted) with Glucophage SR 500 mg prolonged release tablets, Merck Serono, from the UK market as the test product.

Single-dose fasted study, 1000 mg
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting with a wash out period of 7 days between the two administrations. 1 tablet of 1000 mg was administered in each period. 24 male/female subjects participated in the study and 24 subjects completed the study.
Bioequivalence between the test and the reference product was demonstrated since 90% confidence intervals for the log-transformed $AUC_{0\text{-}inf}$ and C_{max} were within the acceptance range of 80-125%.

Single-dose fed study, 1000 mg
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fed conditions with a wash out period of 7 days between the two administrations. 1 tablet of 1000 mg was administered in each period. 24 male/female subjects participated in the study and 24 subjects completed the study.
Bioequivalence between the test and the reference product was demonstrated since 90% confidence intervals for the log-transformed $AUC_{0\text{-}inf}$ and C_{max} were within the acceptance range of 80-125%.

Multiple dose study, 1000 mg
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, multiple dose bioavailability study conducted under fasting with a wash out period of 10 days between the two administrations. 1 tablet of 1000 mg was administered in each period.
24 male/female subjects participated in the study and 22 subjects completed the study.
Bioequivalence between the test and the reference product was demonstrated since 90% confidence intervals for the log-transformed $AUC_{0\text{-}t}$ (24h), C_{min} and C_{max} were within the acceptance range of 80-125%.

Single dose fasted study, 500 mg
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 11 days between the two administrations. 1 tablet of 500 mg was administered in each period. 28 male subjects participated in the study and 25 subjects completed the study.
Bioequivalence between the test and the reference product was demonstrated since 90% confidence intervals for the log-transformed $AUC_{0\text{-}t}$ and C_{max} were within the acceptance range of 80-125%.

Conclusion on bioequivalence studies
Based on the submitted bioequivalence studies Metformin "Actavis PTC" prolonged release tablets is considered bioequivalent with Glucophage SR prolonged release tablets.

The results of the studies with the 500 mg and 1000 mg formulations can be extrapolated to the 750 mg prolonged release tablets, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan & Pharmacovigilance System

Pharmacovigilance system
The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

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 "Actavis PTC".

The summary of safety concerns is as follows, with routine pharmacovigilance and risk minimisation activities only:

Summary of safety concerns	
Important identified risks	• Lactic acidosis • Hepatic insufficiency • Use of metformin before elective surgery • Hypoglycaemia following coadministration with other antidiabetic agents • Hypoglycaemia following coadministration with drugs with intrinsic sympathomimetic activity including glucocorticoids and sympathomimetics • Use in patients with renal impairment • Concomitant use of iodinated contrast media
Important potential risks	None
Important missing information	• Use in children

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 English.
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.

The test consisted of a pilot test with 6 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Metformin “Actavis PTC” 500 mg, 750 mg and 1000 mg prolonged-release tablets has a proven chemical-pharmaceutical quality and is a hybrid of the reference product Glucophage. Glucophage 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.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that a marketing authorisation could be granted. The decentralised procedure was finalised on 14 May 2014. Metformin “Actavis PTC” was authorised in Denmark on 4 July 2014.

The active substance is listed in the published EURD list and the MAH should follow the DLP according to the EURD list.

The date for the first renewal will be: 14 May 2019.

There were no post-approval commitments made during the procedure.