LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pioglitazone Brown
(Pioglitazone hydrochloride)

SE/H/1064/01-03/DC

This module reflects the scientific discussion for the approval of Pioglitazone Brown .The procedure was finalised at 2011-12-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Brown & Burk UK Ltd has applied for a marketing authorisation for Pioglitazone Brown, tablets, 15 mg, 30 mg and 45 mg, claiming essential similarity to Actos, tablets, 15 mg, marketed in the EU by Takeda Global Research and Development Centre (Europe) Ltd. The product contains pioglitazone hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Actos, tablets marketed in the EU by Takeda Global Research and Development Centre (Europe) Ltd.

II. QUALITY ASPECTS

II.1 Introduction

Pioglitazone Brown is presented in the form of tablets containing 15, 30 , 45 mg of pioglitazone which corresponds to 16.54, 33.07, 49.61 mg of the pioglitazone hydrochloride . The excipients are carmellose calcium, hydroxypropylcellulose, lactose monohydrate and magnesium stearate. The tablets are packed in blister pack (Alu/Alu foil) and in high density polyethylene containers with propylene cap.

II.2 Drug Substance

Pioglitazone hydrochloride does not have a monograph in the Ph Eur.

Pioglitazone hydrochloride is a white, crystalline powder which is soluble in N, N-dimethylformamide, slightly soluble in anhydrous ethanol and not very soluble in water. Pioglitazone hydrochloride is having pH dependent solubility and solubility decreases with increasing pH. The structure of pioglitazone hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality and hygroscopcity is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Pioglitazone hydrochloride tablets are formulated using excipients described in the current Ph Eur. The raw materials used in the product are of vegetable origin or have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

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 regards to preclinical data, no further preclinical data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Pioglitazone Brown, 45 mg, tablet with Actos, 45 mg, tablet under fasting conditions. The study was conducted at Accutest research laboratories (India) Private Limited, Navi Mumbai, India between 2009-07-03 and 2009-08-15. Blood samples were collected pre-dose and up to 120 hours post-dose. The study design is considered acceptable. Plasma concentrations of pioglitazone and its metabolite hydroxypioglitzone were determined with an adequately validated LC/MS/MS method. For pioglitazone 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%. From a pharmacokinetic point of view, absence of studies with the additional strength(s) is acceptable, as the pharmacokinetics of pioglitazone is linear between 2 mg and 60 mg.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence

The risk/benefit ratio is considered positive and Pioglitazone Brown, tablets, 15 mg, 30 mg and 45 mg, is recommended for approval.

Commitments
The applicant commit to do process validation study for three batches of all strengths at the proposed maximum commercial batch size of 1,250,000 tablets and for the common blend with maximum size of 450.0 Kg. *However, there is no need to submit the validation study for the proposed maximum commercial batch size if there is no out of specifications or deviations from the result compared to the validation study already submitted.*

VI. APPROVAL

The Decentralised procedure for Pioglitazone Brown, tablets, 15 mg, 30 mg and 45 mg was successfully finalised on 2011-12-01.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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