LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ciprofloxacin Accord
(ciprofloxacin hydrochloride)

SE/H/1026/01-03/DC

This module reflects the scientific discussion for the approval of Ciprofloxacin Accord. Please note that the marketing authorisation was first approved with the name "Ciprofloxacin Intas" and therefore this name is used throughout the document. The procedure was finalised 2011-09-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Intas Pharmaceuticals Limited has applied for a marketing authorisation for Ciprofloxacin Intas, 250 mg, 500 mg and 750 mg, film-coated tablet claiming essential similarity to Ciproxin, 250 mg, 500 mg and 750 mg, film-coated tablet marketed in Sweden by Bayer Schering Pharma AG. The product contains ciprofloxacin hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Ciproxin, 750 mg, tablets marketed by Bayer Plc in UK.

II. QUALITY ASPECTS

II.1 Introduction

Ciprofloxacin Intas is presented in the form of film coated tablets containing ciprofloxacin hydrochloride monohydrate equivalent to 250 mg, 500 mg and 750 mg ciprofloxacin. The excipients are cellulose microcrystalline, croscarmellose sodium, povidone, magnesium stearate, hypromellose, lactose monohydrate, titanium dioxide, macrogol and sodium citrate dihydrate. The film coated tablets are packed in PVC/aluminium blisters.

II.2 Drug Substance

Ciprofloxacin hydrochloride monohydrate has a monograph in the Ph Eur.
Ciprofloxacin hydrochloride monohydrate is a pale yellow, crystalline powder, slightly hygroscopic, soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, in ethyl acetate and in methylene chloride. The structure of ciprofloxacin hydrochloride monohydrate has been adequately proven and its physico-chemical properties sufficiently described. 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

Ciprofloxacin Intas film coated tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product has 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 regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Ciprofloxacin has an oral bioavailability of 70-80 %. Following an oral dose of ciprofloxacin maximal plasma concentrations occur at approximately 1-2 hours. Concomitant administration of the tablet with food has been reported to result in a prolonged time to reach peak serum levels, although overall bioavailability does not appear to be significantly altered. The SPC of the originator states that the product can be taken with or without food. The pharmacokinetics of ciprofloxacin is linear within the dose range 250-1000 mg (Tartaglione et al., 1986; Lettieri et al., 1992, SPC of originator). The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Ciprofloxacin, 750 mg, film-coated tablets manufactured by Intas Pharmaceutical Ltd., India with Ciproxin, 750 mg, tablets under fasting conditions. The study was conducted at Lambda Therapeutic Research Ltd., Navi Mumbai, Maharashtra, India between 20th and 26th February 2009. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of ciprofloxacin were determined with an adequately validated HPLC method with fluorescence detector. 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%. Thus, bioequivalence has been demonstrated for the strength 750 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 Guideline on the Investigation of Bioequivalence.

The risk/benefit ratio is considered positive and Ciprofloxacin Intas, 250 mg, 500 mg and 750 mg, film-coated tablet is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Ciprofloxacin Intas, 250 mg, 500 mg and 750 mg, film-coated tablet was successfully finalised on 2011-09-29.

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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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