LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fluconazole Accord
(Fluconazole)

SE/H/1063/01-04/DC

This module reflects the scientific discussion for the approval of Fluconazole Accord. Please note that the marketing authorisation was first approved with the name "Fluconazole Intas" and therefore this name is used throughout the document. The procedure was finalised at 2012-02-23. 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 Fluconazole Intas, capsule hard, 50 mg, 100 mg, 150 mg and 200 mg, claiming essential similarity to TRIFLUCAN, 50 mg, gélule marketed France by PFIZER HOLDING FRANCE. The product contains fluconazole as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is DIFLUCAN®, 150 mg, cápsulas marketed by VINCI FARMA, S.A. (Grupo Pfizer) in Spain.

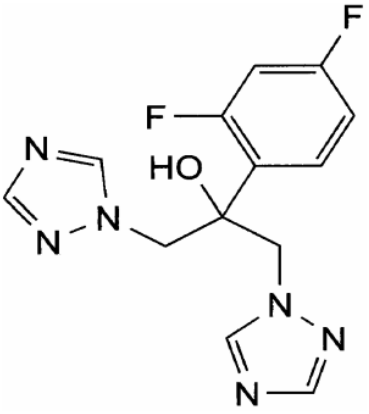
II. QUALITY ASPECTS

II.1 Introduction

The medicinal product Fluconazole Intas is presented in the form of capsules, containing 50 mg, 100 mg, 150 mg or 200 mg of the drug substance fluconazole.

II.2 Drug Substance

The drug substance fluconazole is described in the European Pharmacopeia.

International non-proprietary name (INN):	Fluconazole
Compendial name (Ph. Eur.):	Fluconazole
Chemical names:	2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol 2,4-difluoro-α,α-bis-(1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol
CAS registry number:	86386-73-4
Molecular formula:	$C_{13}H_{12}F_2N_6O$
Relative molecular mass:	306.3
Stereochemistry:	No chiral center
Physical characteristics:	White or almost white, hygroscopic, crystalline powder
Solubility:	Slightly soluble in water, freely soluble in methanol, soluble in acetone
Molecular structure:	

The manufacturer holds a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM). This certificate verifies that the substance is suitably controlled by the monograph "Fluconazole" no. 2287 published in the European Pharmacopeia. The methods used for analysis of the drug substance are those described in the monograph.

A statement from the Qualified Person (responsible for batch release of the finished products) has been provided, confirming that the drug substance fluconazole is manufactured in accordance with Good Manufacturing Practice for active substances.

The stability of the drug substance has been evaluated by the EDQM. A re-test period of 36 months has been established.

II.3 Medicinal Product

Fluconazole Intas capsules are formulated using excipients described in the European Pharmacopeia, except for the colorants which comply with the requirements of Commission Directive 2008/128/EC. Only gelatine and lactose monohydrate are of animal origin. It has been confirmed that these ingredients comply with the note for guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

The pharmaceutical development work has been sufficiently described. *In vitro* dissolution profiles demonstrate pharmaceutical equivalence between Fluconazole Intas and the reference medicinal product Diflucan.

Results from the process validation studies confirm that the manufacturing process is under control and ensure batch to batch reproducibility.

It has been confirmed that all sites involved in the manufacture and control of the medicinal products operate in accordance with Good Manufacturing Practise.

The tests and limits in the release and shelf-life specifications are appropriate to control the quality of the finished product in relation to its intended purpose. The analytical methods have been validated. Batch analysis data demonstrate that the finished products meet the requirements of the specification.

Stability studies under ICH conditions have been performed. The data support a shelf-life of 24 months when stored in the original package below 30°C.

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

Fluconazole has an oral bioavailability of more than 90 %. Following an oral dose of fluconazole maximal plasma concentrations occur at approximately ½ to 1½ hours. The extent of absorption is not affected by food, and therefore there are no restrictions with respect to food in the SPC of the originator. The pharmacokinetics of fluconazole is reported to be linear within the dose range 50-400 mg. The terminal half-life is approximately 30 hours. Fluconazole is mainly excreted renally.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Fluconazole, 150 mg, capsules, manufactured by Intas Pharmaceuticals Limited, India, with Diflucan, 150 mg, capsules, manufactured by Pfizer SA, Madrid, Spain under fasting conditions. The study was conducted at Lambda Therapeutic Research Ltd, Navi Mumbai, India between 11th October and 1st November 2010. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of fluconazole were determined with a validated LC/MS/MS method. For AUC_{0-72h} 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, it is sufficient to study only one strength as the pharmacokinetics of fluconazole is linear between 50 and 400 mg. The applicant has submitted a study with the strength 150 mg instead of the highest strength 200 mg, which is acceptable since fluconazole is highly soluble.

IV.2 Discussion on the clinical aspects

Fluconazole is an oral antimycotic drug that has been widely used for many years and the clinical experience is therefore extensive. 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
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging layout report making reference to Ciprofloxacin Intas. The bridging report submitted by the applicant has been found acceptable.

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 (CHMP/QWP/EWP/1401/98 Rev. 1)

The risk/benefit ratio is considered positive and Fluconazole Intas, capsule hard, 50 mg, 100 mg, 150 mg and 200 mg, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Fluconazole Intas, capsule hard, 50 mg, 100 mg, 150 mg and 200 mg, was successfully finalised on 2012-02-23.

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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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