CBG MEB

# Public Assessment Report

# Scientific discussion

# Itraconazol Actavis 100 mg, capsules, hard

# (itraconazole)

## NL License RVG: 107049

## Date: 9 March 2015

**This module reflects the scientific discussion for the approval of Itraconazol Actavis 100 mg, capsules, hard. The marketing authorisation was granted on 11 September 2013. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Itraconazol Actavis 100 mg, capsules, hard from Actavis B.V.

The product is indicated for
- Vulvovaginal candidiasis, oral candidiasis, dermatomycoses caused by dermatophytes, yeasts, and pityriasis versicolor,
- lymphocutaneous sporotrichosis, paracoccidioidomycosis, blastomycosis (in immunocompetent patients) and histoplasmosis
- Itraconazole can be used to treat patients suffering from systemic aspergillosis who were found to be refractory or intolerant to adequate standard treatment with amphotericin
- Onychomycoses caused by dermatophytes and/or yeasts.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Trisporal 100 mg, capsules (NL License RVG 13224), which has been registered in the Netherlands by Janssen-Cilag B.V. since 15 October 1990.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Itraconazol Actavis 100 mg is a hard gelatin capsule with an opaque green cap and body containing yellowish-beige spherical microgranules.

The capsules are packed in Al/PVC-LDPE-PVDC blisters.

The excipients are:
Capsule content: hypromellose (E464), poloxamer, sugar spheres (maize starch and sucrose)
Capsule shell: quinoline yellow (E104), gelatin, indigo carmine (E132), titanium dioxide (E171)

## II.2 Drug Substance

The active substance is itraconazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off white powder, which is practically insoluble in water, freely soluble in methylene chloride and very slightly soluble in ethanol. Itraconazole has a chiral carbon in its structure.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. monograph for itraconazole and the additional CEP requirements. The specification is acceptable in view of the CEP and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches from both production sites.

Stability of drug substance
Stability data on the active substance have been provided for 19 full-scale batches stored at 25°C/60% RH (5 years) and 40°C/75% RH (6 or 9 months). The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Itraconazole capsules are hard gelatine capsules filled with pellets. The pellets consist of a sugar core, an active coating using hypromellose and a protective coating with the aid of poloxamer.
The bioequivalence study was performed versus the Spanish innovator product, Sporanox. Dissolution profiles comparing the Dutch innovator product Trisporal versus the Spanish innovator product are presented. The comparative release profiles of the two innovators are comparable, with no significant differences.
The dissolution profile of Itraconazol Actavis 100 mg was compared to the product used in the bioequivalence study. The dissolution profiles are comparable.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
Sugar spheres are loaded with itraconazole and excipients solution. Once the microgranules have been sieved, an antistatic excipient is added to facilitate capsule filling-process. The pellets are analysed and encapsulated in hard gelatin capsules. In-process controls are identified and specifications are set.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full-scale batches for the manufacturing process of the microgranules and for 3 full-scale batches for the capsule filling process.
The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. For the hard capsules of gelatine in house specifications are set. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, capsule net weight, identification, assay, water content, disintegration, dissolution test, impurities, microbial control and uniformity of dosage units. End of shelf-life specifications are set and differ from the release specifications for the impurities and dissolution tests. The analytical methods have been adequately described and validated.
Batch analytical data of three production-scale batches have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu/Alu thermoformed blister packs.
The stability results show that after 6 months of storage at accelerated conditions ‘any other single impurity’ is out of specification, for all three batches. Furthermore there is a negative trend in the dissolution rate.

At intermediate conditions 'any other single impurity' is on the upper limit for all three batches after 12 months of storage. A negative trend for dissolution is also observed but less pronounced. The results of a photostability study showed that the product is not sensitive to light.
At long term conditions (25°C/60% RH) all parameters stay within specification after 24 months of storage. A shelf-life of 2 years can be granted, if stored below 25°C in the proposed packaging.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Itraconazol Actavis 100 mg, capsules, hard has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Itraconazol Actavis 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.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Trisporal, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Itraconazole is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

### IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Itraconazol Actavis 100 mg (Actavis B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Sporanox 100 mg capsules (Janssen-Cilag, Spain).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the Dutch and Spanish reference products.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

*Design*
A four-period, two sequence, cross-over, controlled, randomized, replicate design bioequivalence study was carried out under fed conditions in 40 healthy subjects, 14 females and 26 males, aged 18 - 43 years. Each subject received a single dose (100 mg) of one of the 2 itraconazole formulations. The capsules were administered in solid form with 200 ml water within 30 min after start of inatke of a standardised breakfast, consisting of 1 omelette (2 eggs + 10 g butter), 1 croissant + 10 g butter and 200 ml whole milk. For each subject there were 4 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

The study design is considered adequate. Fed conditions were applied , because itraconazole should be taken with food, as concomitant food intake will increase absorption, which is agreed.
A replicate design was used to deal with the known high intra-subject variability for itraconazole. Scaling based upon the observed variability has been applied as approach for bioequivalence testing, next to the use of unscaled data.
Next to the parent itraconazole, also OH-itraconazole was analysed. As for itraconazole bioequivalence should be proven upon parent data, the data for the OH-metabolite were not taken into account.

*Analytical/statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
Two subjects dropped out: one subject withdrew for personal reasons and one subject was withdrawn because of an adverse event. Thirty-eight subjects completed the study entirely, and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of itraconazole under fed conditions.

| **Treatment N=38** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 760 ± 480 | 825 ± 505 | 73 ± 39 | 4.5 (3.0 – 8.0) | 17 ± 10 |
| **Reference** | 811 ± 465 | 879 ± 487 | 76 ± 39 | 4.5 (2.0 – 7.0) | 18 ± 10 |
| ***Ratio (90% CI)** | 0.93 (0.82-1.05) | -- | 0.96 (0.86-1.08) | -- | -- |
| **CV (%)** | -- | -- | -- | -- | -- |

**$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity
**$AUC_{0-t}$** area under the plasma concentration-time curve from time zero to t hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life

**ln-transformed values*

Conclusion on bioequivalence study
The observed intra-subject variability for itraconazole for reference is 55% for $AUC_{0-t}$ and 49% for $C_{max}$. Based on the pharmacokinetic parameters of itraconazole, the Itraconazol Actavis and Sporanox

100 mg capsules are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and $C_{max}$ of itraconazole were inside the normal range of acceptability (0.80 – 1.25). As the unscaled data show bioequivalence for test and reference, scaled data are not reported.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

### IV.3 Risk Management Plan

The MAH did not submit a risk management plan, as it was not required at the time the application was made. This is acceptable. Itraconazole is a well known active substance.
The MAH has a pharmacovigilance system in place, in compliance with the applicable guidelines.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Trisporal. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. This generic medicinal product can be used instead of the reference product.

## 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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

Itraconazol Actavis 100 mg, capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Trisporal capsules 100 mg, capsules. Trisporal 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 Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Itraconazol Actavis with the reference product, and have therefore granted a marketing authorisation. Itraconazol Actavis 100 mg capsules, hard was authorised in the Netherlands on 11 September 2013.

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

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|
| MA transfer and name change. | IB | 22-07-2013 | 12-9-2013 | Approval | No |
| Change in the Pharmacovigilance System Master File (PSMF). | IA | 10-7-2014 | 17-7-2014 | Approval | No |