Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

LOZANOC 50 MG HARD CAPSULES

(Itraconazole)

Procedure No: UK/H/4345/001/DC

UK Licence No: PL 37190/0001

MAYNE PHARMA UK LIMITED

LAY SUMMARY

On 20 December 2012, Germany, Spain, Sweden and the UK agreed to grant a Marketing Authorisation to Mayne Pharma UK Limited for the medicinal product Lozanoc 50 mg hard capsules (PL 37190/0001; UK/H/4345/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 28 January 2013. This is a prescription-only medicine (POM).

Lozanoc 50 mg hard capsules contains the active ingredient itraconazole which belongs to a group of medicines called 'antimycotics for systemic use', also called anti-fungal medicines.

Lozanoc 50 mg hard capsules are used to treat fungal infections, including those caused by yeasts. These infections may affect:

- the vagina (thrush)
- the skin
- the lungs
- the mouth
- the nails
- internal organs

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Lozanoc 50 mg hard capsules outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Lozanoc 50 mg hard capsules
Type of Application	Hybrid, Article 10.3
Active Substances	Itraconazole
Form	Hard capsule
Strength	50 mg
MA Holder	Mayne Pharma UK Limited 66 Lincoln's Inn Fields London WC2A 3LH United Kingdom
Reference Member State (RMS)	UK
CMS	Germany, Spain and Sweden
Procedure Number	UK/H/4345/001/DC
Timetable	Day 210 – 20 December 2012

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4
Labelling

The following text is the approved labelling text as agreed during the decentralised procedure. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - Blisters

1. NAME OF THE MEDICINAL PRODUCT

LOZANOC 50 mg hard capsules
itraconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of itraconazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4 hard capsules
6 hard capsules
15 hard capsules
18 hard capsules
30 hard capsules
60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take as directed by your doctor.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

One hard capsule of LOZANOC 50 mg corresponds to one 100 mg of conventional itraconazole hard capsules. Always take this medicine exactly as your doctor has told you.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from light and moisture.
Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mayne Pharma UK Limited
66 Lincoln's Inn Fields
London WC2A 3LH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL36029/0001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LOZANOC

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FOILS - blisters

1. NAME OF THE MEDICINAL PRODUCT

LOZANOC 50 mg hard capsules
itraconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mayne Pharma UK Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - Bottles

1. NAME OF THE MEDICINAL PRODUCT

LOZANOC 50 mg hard capsules
itraconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of itraconazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

15 hard capsules
30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take as directed by your doctor.
Please read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

One hard capsule of LOZANOC 50 mg corresponds to one 100 mg of conventional itraconazole hard capsules. Always take this medicine exactly as your doctor has told you.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Store in the original package in order to protect from light and moisture.

Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mayne Pharma UK Limited

66 Lincoln's Inn Fields

London WC2A 3LH

United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 37190/0001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LOZANOC

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - Bottles

1. NAME OF THE MEDICINAL PRODUCT

LOZANOC 50 mg hard capsules

itraconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of itraconazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

15 hard capsules

30 hard capsules

60 hard capsules

90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take as directed by your doctor.

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

Store in the original package in order to protect from light and moisture.

Keep the container in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mayne Pharma UK Limited

66 Lincoln's Inn Fields

London WC2A 3LH

United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 37190/0001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable for Immediate Packaging units

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Lozanoc 50 mg hard capsules (PL 37190/0001; UK/H/4345/001/DC) could be approved. This application was submitted by the decentralised procedure, with the UK as Reference Member State (RMS), and Germany, Spain and Sweden as Concerned Member States (CMS). This is a prescription-only medicine (POM).

Lozanoc 50 mg hard capsules are indicated for:

- Superficial mycoses
  Itraconazole is indicated-if external treatment is not effective or not appropriate-for the treatment of the following fungal infections: dermatomycoses (e.g. tinea corporis, tinea cruris, tinea pedis, tinea manus) and Pityriasis versicolor.

- Systemic mycoses
  Itraconazole is indicated for the treatment of systemic mycoses, such as candidiasis, aspergillosis, and histoplasmosis.

This application is made via the Decentralised Procedure (DCP), according to Article 10.3 of 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Sporanox 100mg Capsules which was first authorised in the UK to Janssen-Cilag Ltd on 18 January 1989 (PL 00242/0142).

This application was referred to the Commission on Human Medicines (CHM) who met in December 2011 and June 2012 for consideration of whether the safety, quality and efficacy of the product were demonstrated. Following consideration of the applicant's responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

Itraconazole is a triazole derivative which is used for the short term and long term treatment of a number of different fungal infections.

The pharmacokinetics of itraconazole has been investigated in healthy subjects, special populations and patients after single and multiple dosing. In general, Itraconazole is rapidly absorbed. Peak plasma concentrations are reached within 2 to 5 hours after oral administration. Itraconazole is extensively metabolised by the liver into a large number of metabolites. The main metabolite is hydroxy-itraconazole, with plasma concentrations about twice those of unchanged itraconazole. The mean elimination half-life of itraconazole is about 17 hours after a single dose and increases to 34-42 hours after repeated dosing. Itraconazole has non-linear pharmacokinetics, and consequently itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with C_{max} values 0.5 μg/ml, 1.1 μg/ml and 2.0 μg/ml after oral administration of 100 mg once daily, 200 mg once daily, and 200 mg twice daily, respectively. Plasma levels are undetectable 7 days after suspending itraconazole treatment. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism. Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with faeces.

No new non-clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to a product that has been licensed for over 10 years.

To support the application, the Marketing Authorisation Holder (MAH) submitted one clinical efficacy and safety study for the treatment of onychomycosis of the toenail and two bioequivalence studies (a single dose study in the fed and fasting state and a single dose study in the fed state) comparing the test product Lozanoc 50 mg hard capsules (Mayne Pharma UK Limited) with the reference product Sporanox 100mg Capsules (Janssen-Cilag Ltd). The studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 20 December 2012. After a subsequent national phase, the licence was granted in the UK on 28 January 2013.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Lozanoc 50 mg hard capsules
Name(s) of the active substance(s) (INN)	Itraconazole
Pharmacotherapeutic classification (ATC code)	Antimycotic for systemic use, triazole derivative (J02AC02).
Pharmaceutical form and strength(s)	Hard capsule
Reference numbers for the Mutual Recognition Procedure	UK/H/4345/001DC
Reference Member State	United Kingdom
Member States concerned	Germany, Spain and Sweden
Marketing Authorisation Number(s)	PL 37190/0001
Name and address of the authorisation holder	Mayne Pharma UK Limited 66 Lincoln's Inn Fields London WC2A 3LH United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

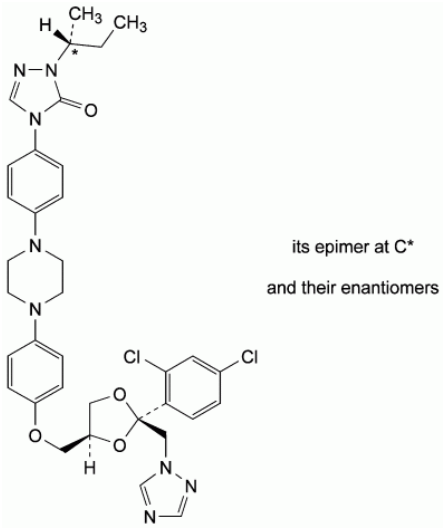
III.1 QUALITY ASPECTS

S. Active substance

INN: Itraconazole

Chemical name: 4-[4-[4-[4-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1RS)-1-methylpropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

Structure:



Molecular formula: $C_{35}H_{38}C_{12}N_8O_4$

Molecular weight: 706.0

Appearance: Itraconazole is a white to off-white powder.

Solubility: Itraconzaole is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in tetrahydrofuran (THF) and very slightly soluble in alcohol.

Itraconazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance itraconazole are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients hypromellose phthalate, sodium starch glycolate (type A), anhydrous colloidal silica , magnesium stearate, gelatin, Brilliant blue FCF (E133), titanium dioxide (E171) and black printing ink SW-9008 (consisting of shellac, potassium hydroxide, black iron oxide (E172), and purified water).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Brilliant blue FCF (E133), titanium dioxide (E171) and black printing ink SW-9008 which are controlled to suitable in-house specifications. In addition, the colourings Brilliant blue FCF (E133), titanium dioxide (E171) and black iron oxide (E172) [present in the black printing ink] are in compliance with current EU Directives concerning the use of colouring agents. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate stable, robust, hard capsules containing 50 mg itraconazole, which could be considered a hybrid of the reference product Sporanox 100mg Capsules (Janssen-Cilag Ltd)

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results. The MAH has committed to perform additional process validation on future commercial scale batches.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in:

- Aluminium (foil/foil) blister and Triplex blisters in pack sizes of 4, 6, 15, 18, 30 and 60 capsules.
- High density polyethylene (HDPE) bottles with white polypropylene (PP) child resistant cap and heat seal liner in pack sizes of 15, 30, 60 and 90 capsules.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the blister packs and 3 years for the HDPE bottles with the storage conditions ‘ Do not store above 25°C. Store in the original package in order to protect from light and moisture.’

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains

MAA forms
The MAA form is satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of itraconazole are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

The MAH has not conducted an in depth environmental risk assessment (ERA) in accordance with regulatory guidelines (EMEA/CHMP/SWP/4447/00). This is acceptable as the risks to the environment are not expected to increase as the proposed product will be used to substitute for the originator product.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Clinical Pharmacology

The clinical pharmacology of itraconazole is well-known. With the exception of the clinical studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics

In support of this application, the marketing authorisation holder has submitted the following bioequivalence studies:

STUDY HGN007

A single-dose, four-way crossover, relative bioavailability study to compare the pharmacokinetics of the test product Lozanoc 50 mg hard capsules (Mayne Pharma UK Limited) versus the reference product Sporanox 100mg Capsules (Janssen-Cilag Ltd) in healthy adult volunteers under fed and fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 50 mg (test) or 100 mg capsule (reference). Volunteers were provided a meal at least 10 hours prior to dosing for the fasting period and a high fat meal 30 minutes prior to dosing for the fed period. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for itraconazole in the fed and fasted state are presented below (log-transformed values; geometric least squares mean and 90% confidence intervals):

Parameter	Geometric LS mean: 50 mg SUBA®-itraconazole (fasted)	Geometric LS mean: 100 mg Sporanox® (itraconazole) (fasted)	Ratio of geometric LS means SUBA® : Sporanox® (90% CI)
$AUC_{0\text{-}tlast}$ (ng.h/mL)	448	733	0.611 (0.557, 0.670)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	591	866	0.682 (0.629, 0.740)
C_{max} (ng/mL)	63.4	63.8	0.993 (0.859, 1.15)
t_{max}[a] (h)	2.5	2.5	0 (-0.500, 0.258)

[a] Median difference (SUBA®-itraconazole – Sporanox® [Itraconazole])

Parameter	Geometric LS mean: 50 mg SUBA®-itraconazole (fed)	Geometric LS mean: 100 mg Sporanox® (itraconazole) (fed)	Ratio of geometric LS means SUBA® : Sporanox® (90% CI)
$AUC_{0\text{-}tlast}$ (ng.h/mL)	359	358	1.00 (0.827, 1.22)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	521	591	0.883 (0.774, 1.05)
C_{max} (ng/mL)	33.6	36.2	0.927 (0.763, 1.12)
t_{max}[a] (h)	6	5	1.98 (0.500, 2.75)

[a] Median difference (SUBA®-itraconazole – Sporanox® [Itraconazole])

Parameter	Geometric LS mean: 50 mg SUBA®-itraconazole (fasted)	Geometric LS mean: 100 mg Sporanox® (itraconazole) (fed)	Ratio of geometric LS means SUBA® : Sporanox® (90% CI)
$AUC_{0\text{-}tlast}$ (ng.h/mL)	451	358	1.26 (1.03, 1.54)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	650	593	1.10 (0.925, 1.30)
C_{max} (ng/mL)	63.6	36.2	1.76 (1.44, 2.14)
t_{max}[a] (h)	2.5	5	-2.50 (-3.00, -1.98)

a Median difference (SUBA®-itraconazole fasted – Sporanox® [Itraconazole] fed)

$AUC_{0\text{-}t\ last}$	area under the plasma concentration-time curve from time zero to t last hours
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time zero to infinity.
C_{max}	maximum plasma concentration
T_{max}	Time maximum plasma concentration is reached

SUBA=Test product
Sporanox=Reference product

In the fed state, the test and the reference show that the 90% confidence interval for the ln-transformed AUC lies within the acceptance criteria of 80-125% but C_{max} lies outside.

The C_{max} for the test and reference in the fasting and fed states are similar suggesting the 50mg test has similar initial absorption as the 100mg reference probably due to higher bioavailability of the test. The AUC for the test and reference in the fed state is similar but AUC is very different in the fasting state. The difference in AUC in the fasted and fed state for the test is much less compared to the reference.

On comparing the test in the fasting state versus (vs) reference in the fed state, the AUC of test is only slightly higher than the reference and the C_{max} is almost twice despite the strength of the test being half that of the reference.

According to published literature, itraconazole absorption is promoted by low stomach pH, long gastric retention time and a high fat content of the coadministered meal. According to the SmPC of Sporanox, the capsules should be taken immediately after a meal since food maximises absorption, and absorption is almost completed when taken after food although there is a high inter-individual variability.

However in this study, the absorption of itraconazole in the fasting state is higher than that in the fed state for both the test and the reference.

Considering the C_{max} and AUC of the test in the fed and fasting state, it appears there is less pronounced food effect with quick and early absorption in the fasting state but slower and longer absorption in the fed state (AUC similar in the two states but Cmax higher in fasted than fed state).

Based on the submitted bioequivalence study, the test and reference products, after a single dose (50mg test vs 100mg reference) administration, are considered **not** to be bioequivalent.

STUDY HGN008
A randomised, open-label, two-treatment, four-period, two-sequence, replicate-design, crossover study to compare the pharmacokinetics of the test product Lozanoc 50 mg hard capsules (Mayne Pharma UK Limited) versus the reference product Sporanox 100mg Capsules (Janssen-Cilag Ltd) in healthy adult volunteers under fed conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 50 mg (test) or 100 mg capsule (reference). Volunteers were provided a high fat meal 30 minutes prior to dosing for the fed period. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for itraconazole in the fed state are presented below (log-transformed values; geometric least squares mean and 90% confidence intervals):

Table 11-4: Bioequivalence Analysis of the Pharmacokinetic Parameters of Itraconazole Following Administration of 50 mg SUBA®-itraconazole and 100 mg Sporanox® (Itraconazole) in the Fed Condition

Parameter	Geometric LS mean		Ratio (50 mg SUBA® capsule fed: 100 mg Sporanox® capsule fed) (90% CI)	Within-subject CV% (90% CI)	
	50 mg SUBA® capsule fed	100 mg Sporanox® capsule fed		50 mg SUBA® capsule fed	100 mg Sporanox® capsule fed
AUC_{0-72h} (ng.h/mL)	536	692	0.774 (0.696, 0.861)	20.9 (17.4, 26.3)	44.8 (36.9, 57.6)
$AUC_{0-tlast}$ (ng.h/mL)	479	602	0.797 (0.704, 0.901)	27.8 (23.6, 34.0)	51.2 (43.1, 63.7)
$AUC_{0-\infty}$ (ng.h/mL)	611	800	0.763 (0.678, 0.859)	22.2 (18.1, 29.3)	47.4 (38.7, 62.1)
C_{max} (ng/mL)	41.3	52.6	0.785 (0.695, 0.888)	33.3 (28.3, 40.9)	35.5 (30.1, 43.5)

$AUC_{0-t\ last}$	area under the plasma concentration-time curve from time zero to t last hours
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to t 72 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity**.**
C_{max}	maximum plasma concentration
T_{max}	Time maximum plasma concentration is reached
SUBA=Test product	
Sporanox=Reference product	

The C_{max} and AUC lie outside the 80-125% CI. According to the guidelines, based on the variability, the interval can be widened for the C_{max} but not for AUC. As the CV was more than 35% for the reference the interval can be widened for C_{max} only.

Based on the submitted bioequivalence study, the test and reference products, after a single dose (50mg test vs 100mg reference) administration, are considered **not** to be bioequivalent.

As bioequivalence was not demonstrated in the above studies, the Marketing Authorisation Holder (MAH) has also submitted the following clinical efficacy and safety study in support of this application:

Efficacy and Safety Study
STUDY 70850702
A randomised, double-blind, multiple-site, placebo-controlled study, comparing the efficacy and safety of Lozanoc 50 mg hard capsules (Mayne Pharma UK Limited) with Sporanox 100mg Capsules (Janssen-Cilag Ltd) in the treatment of onychomycosis of the toenail. Both the test and the reference formulations were compared to a placebo formulation to test for superiority.

Volunteers were randomly assigned in a 3:3:1 ratio to the test formulation (2 x 50 mg capsules) once a day, reference formulation 200 mg (2 x 100 mg capsules) once a day, or placebo (2 x capsules) once a day for 12 weeks of treatment.

Analyses sets

Efficacy populations

Intent-to-Treat (ITT) Population
The ITT population included all patients that met all the inclusion/exclusion criteria; positive baseline mycological culture, dosed with the study drug at least once and had at least one post-baseline evaluation.

A patient was considered a Therapeutic Cure if they were both a Clinical Cure (NIRS of 0) and a Mycological Cure (negative KOH and mycological culture). Any patient who was discontinued from the study prior to Visit 7 because of lack of efficacy was automatically considered a Clinical Failure and thus a Therapeutic Failure.

Safety Population
The Safety Population included all patients who were randomised.

Definitions

Nail Infection Rating Scale (NIRS)

The following definitions were used to define the severity of each of the clinical signs and symptoms in the NIRS. If at Visit 1 (baseline) more than one toenail was infected the toenail with the highest NIRS score was identified and used for the Visit 1 and all future determinations. The toenail was designated the "Target Nail".

Onychomycosis
o = Less than 10% of the nail was missing or detached
1 = 10 %-49 % of the nail was missing or had become detached
2 =50 % or more but less than 75 % of the nail was missing or had detached
3 =75 % or more of the nail was missing or detached

Hyperkeratosis
o = Absence of any signs of subungual thickening that could be attributed to onychomycosis
1 = 10-49 % of the nail shows signs of subungual thickening
2 =50-74% of the nail shows signs of subungual thickening
3 =75 % or more of the nail shows signs of subungual thickening

Discoloration
o = No discoloration of the nail that is consistent with onychomycosis infection
1 = Minor discoloration in or beneath the nail but not readily noticeable or extensive
2 = Nail is clearly discoloured with white/yellow or orange brown patches covering 50%-75% of the nail
3 =More than 75 % of the toenail is clearly discoloured.

Outcomes/ endpoints

Efficacy Assessments

Primary efficacy assessments

The three primary endpoints of the study were the proportion of patients in each treatment group who were considered a Therapeutic Cure, Clinical Cure and Mycological Cure at the End of Study Visit (week 24).

Secondary efficacy assessments

The proportion of patients in each treatment group who were considered a Therapeutic Cure, Clinical Cure and Mycological Cure at the End of Treatment Visit (week 12) and the proportion of patients in each treatment group who during the study were considered a Mycological Cure and then relapsed prior to the end of the study and showed a re-infection (Week 24).

All primary and secondary endpoints were tested for superiority against Placebo. The ITT was used for all analyses of non-inferiority and superiority.

Statistical Analysis

Primary efficacy analysis:
There were 3 primary endpoints. Non-inferiority was determined by evaluating the proportion of patients in each treatment group who were:
1) a Therapeutic Cure at the End of Study Visit (Week 24)
2) a Clinical Cure at the End of Study Visit (Week 24)
3) a Mycological Cure at the End of Study Visit (Week 24)

The superiority of the Test and Reference formulations against the Placebo was tested using the same 3 dichotomous end points. For the three primary endpoints and all four dichotomous secondary endpoints, if the difference between the proportion of patients considered a cure in the Test or Reference group was statistically greater ($p < 0.05$) than the proportion of patients considered a cure in the Placebo group, then superiority of that treatment over placebo was considered to have been demonstrated. A one-sided continuity corrected Z-test was used for superiority testing.

The ITT was used for all analysis of superiority. If the lower bound 95% confidence interval of the difference between the proportion of patients in the Test group compared to the Reference group considered a Therapeutic Cure, Clinical Cure or Mycological Cure as appropriate at week 24 was greater than the predefined non-inferiority margin then non-inferiority was considered to have been demonstrated.

Secondary efficacy analysis:
For all parameters if the lower bound 95% confidence interval of the difference between the proportion of patients in the Test group compared to the Reference group considered a Therapeutic Cure, Clinical Cure or Mycological Cure as appropriate at week 12 was greater than the predefined non-inferiority margin then non-inferiority was considered to have been demonstrated.

Results
Efficacy analysis
Primary efficacy variables

Primary Analysis – Non Inferiority Intent-to-Treat Population (ITT)				
Therapeutic Cure at Visit 7 (Week 24)				
		Therapeutic Cure	**Difference**	**Lower 95% CI**
Test		8 (10.53%)	6.47	-1.77
Ref		3 (4.05%)		
Clinical Cure at Visit 7 (Week 24)				
		Clinical Cure	**Difference**	**Lower 95% CI**
Test		12 (15.79%)	10.38	0.92
Ref		4 (5.41%)		
Mycological Cure at Visit 7 (Week 24)				
		Mycological Cure	**Difference**	**Lower 95% CI**
Test		25 (32.89%)	3.17	-10.62
Ref		22 (29.73%)		

Primary Analysis - Superiority (ITT)				
Therapeutic Cure at Visit 7 (Week 24)				
		Therapeutic Cure	**Comparison**	**One sided p-value**
Test		8 (10.53%)	Test v. Placebo	p = 0.0135*
Ref		3 (4.05%)	Ref v. Placebo	p = 0.2861
Placebo		0 (0.00%)		
Clinical Cure at Visit 7 (Week 24)				
		Clinical Cure	**Comparison**	**One sided p-value**
Test		12 (15.79%)	Test v. Placebo	p = 0.0009*
Ref		4 (5.41%)	Ref v. Placebo	p = 0.1570
Placebo		0 (0.00%)		
Mycological Cure at Visit 7 (Week 24)				
		Mycological Cure	**Comparison**	**One sided p-value**
Test		25 (32.89%)	Test v. Placebo	p = 0.0001*
Ref		22 (29.73%)	Ref v. Placebo	p = 0.0003*
Placebo		1 (4.17%)		

*Statistically significant if p<0.05

Secondary efficacy variables

Secondary Analysis – Non Inferiority (ITT)				
Therapeutic Cure at Visit 6 (Week 12)				
		Therapeutic Cure		
Test		0 (0.00%)		
Ref		0 (0.00%)		
Clinical Cure at Visit 6 (Week 12)				
		Clinical Cure	**Difference**	**Lower 95% CI**
Test		1 (1.32%)	1.32	-2.17
Ref		0 (0.00%)		
Mycological Cure at Visit 6 (Week 12)				
		Mycological Cure	**Difference**	**Lower 95% CI**
Test		16 (21.05%)	-0.57	-12.91
Ref		16 (21.62%)		
Mycological Relapse Between Treatment Groups (Visit 6 to Visit 7)				
		Relapse	**Difference**	**Lower 95% CI**
Test		3 (18.75%)	-6.25	-36.47
Ref		4 (25.00%)		

Secondary Analysis - Superiority (ITT)				
Therapeutic Cure at Visit 6 (Week 12)				
		Therapeutic Cure		
Test		0 (0.00%)		
Ref		0 (0.00%)		
Placebo		0 (0.00%)		
Clinical Cure at Visit 6 (Week 12)				
		Clinical Cure	**Comparison**	**One sided p-value**
Test		1 (1.32%)	Test v. Placebo	p = 0.1377
Ref		0 (0.00%)		
Placebo		0 (0.00%)		
Mycological Cure at Visit 6 (Week 12)				
		Mycological Cure	**Comparison**	**One sided p-value**
Test		16 (21.05%)	Test v. Placebo	p = 0.2396
Ref		16 (21.62%)	Ref v. Placebo	p = 0.2210
Placebo		3 (12.50%)		
Mycological Relapse Between Treatment Groups (Visit 6 to Visit 7)				
		Relapse	**Comparison**	**One sided p-value**
Test		3 (18.75%)	Test v. Placebo	p = 0.0096*
Ref		4 (25.00%)	Ref v. Placebo	p = 0.0179*
Placebo		2 (66.67%)		

*Statistically significant if p<0.05

For this study design it is first appropriate to establish whether the test and reference products can be considered superior to placebo. At Week 24 the test product was superior to placebo in terms of therapeutic cure, clinical cure and mycological cure. However, the reference product was not superior to placebo for therapeutic cure or clinical cure although superiority for the reference product was clearly established for mycological cure. It is noted that the therapeutic and clinical cure rate at Week 12 in all three treatment groups was nearly zero.

The fact that superiority to placebo was established for the test, but not the reference, product is relevant to inferences that can be made in terms of non-inferiority. Formally as the reference product was not shown to be superior to placebo, conclusions about non-inferiority of the test product to the reference product cannot be made.

Results were also analysed for cure rates at interim visits (weeks 6 and 8) at which point there were no patients with therapeutic or clinical cure but some patients with mycological cure with results in favour of the test.

Overall the results of this study provide convincing evidence that the test product is superior to placebo. Due to the fact that the reference product was not shown to be superior to placebo it is not possible to draw any definite conclusions about the relative efficacy of the test and reference products. Lower C_{max} and AUC levels were observed in the pharmacokinetic studies of the test product compared to the reference product.

Comparison of AUC/MIC ratios and relationship to clinical efficacy
Reflected by the range of approved indications for the reference product (Sporanox® 100mg Capsules) in the UK and throughout the EU, itraconazole has been used to treat a wide variety of fungal infections since its first introduction into clinical practice.

For instance, with both the 100 mg capsule (Sporanox®) form of itraconazole and the oral solution, there are data in oropharyngeal candidosis to establish a relationship between minimum inhibitory concentration (MIC) value, serum level and clinical response (Cross, Bagg et al. 2000). This work supports the establishment of proposed break points for predicting clinical responses for candidosis (Rex, Pfaller et al. 1997).

In aspergillosis it has been more difficult to establish a relationship between MIC values and clinical responses given that many infections also occur in the context of severe immunosuppression leading to greater unpredictability. However, in a murine model of aspergillosis a similar positive predictive value of MIC determination and clinical response was seen (Denning, Radford et al. 1997). Notably, some strains of *Aspergillus fumigatus* show MIC values at the upper range. However, resistance to triazole antifungals occurs in fewer than 2% of strains and there is evidence that there is cross resistance between itraconazole, posaconazole and voriconazole (Pfaller, Boyken et al. 2011).

The MAH acknowledges that there is limited evidence for a relationship between MIC level and clinical breakpoints for other systemic infections, such as histoplasmosis. However, the authors of the US Infectious Disease society guidelines advise that the relationship between the low MICs for Histoplasma capsulatum and its clinical efficacy were sufficiently consistent to continue to recommend this drug as primary treatment of histoplasmosis.

Given:

(i) Oral itraconazole has been successfully used for decades to treat a wide range of superficial and systemic fungal infections
(ii) Lozanoc 50 mg hard capsules and Sporanox® 100 mg Capsules contain the same drug substance

The goal of a comparison of AUC/MIC ratios for the two formulations is not to predict the clinical efficacy of itraconazole, rather is it to assess:

- The probability that a Lozanoc 50 mg hard capsules patient will achieve a lower exposure than is necessary for therapeutic effect compared to the corresponding probability with Sporanox® 100 mg Capsules.
- The probability that a Lozanoc 50 mg hard capsules patient will achieve a much greater exposure than is necessary compared to the corresponding probability with Sporanox® 100 mg Capsules.

The table below lists the typical infecting organisms for specific mycoses that theoretically fall within the proposed indication for this application (superficial and systemic mycoses) and their corresponding MIC ranges:

Table 21: MIC Ranges per indication and infecting organism

INDICATIONS		INFECTING ORGANISM	MIC RANGE
Superficial mycoses			
Dermatomycoses	tinea corporis	*Trichophyton sp. (rubrum, tonsurans interdigitale, mentagrophytes, concentricim, violaceum et al.)*	0.01-8 MIC_{90}= 0.25-0.5
		Microsporum sp. (canis, gypseum, et al.)	0.01-4 MIC_{90}= 0.25-0.5
		Epidermophyton floccosum	0.01-8 MIC_{90}= 0.125
	tinea cruris	*Trichophyton sp. (rubrum, tonsurans interdigitale, mentagrophytes, et al.)*	0.01-8 MIC_{90}= 0.25-0.5
		Microsporum sp. (canis, et al.)	0.01-4 MIC_{90}= 0.25-0.5
		Epidermophyton floccosum	0.01-8 MIC_{90}= 0.125
	tinea pedis	*Trichophyton sp. (rubrum, tonsurans interdigitale, mentagrophytes, et al.)*	0.01-8 MIC_{90}= 0.25-0.5
		Microsporum sp. (canis, gypseum, et al.)	0.01-4 MIC_{90}= 0.25-0.5
		Epidermophyton floccosum	0.01-8 MIC_{90}= 0.125
	tinea manuum	*Trichophyton sp. (rubrum, interdigitale, mentagrophytes.)*	0.01-8 MIC_{90}= 0.25-0.5
		Epidermophyton floccosum	0.01-8 MIC_{90}= 0.125
	tinea unguium	*Trichophyton sp. (rubrum, tonsurans interdigitale, mentagrophytes, et al.)*	0.01-8 MIC_{90}= 0.25-0.5
		Microsporum sp. (canis, et al.)	0.01-4 MIC_{90}= 0.25-0.5
		Epidermophyton floccosum	0.01-8 MIC_{90}= 0.125
	tinea capitis	*Trichophyton sp. (tonsurans, violaceum, soudanense, schoenleinii, mentagrophytes, verrucossum , et al.)*	0.01-8; MIC_{90}= 0.25-0.5
		Microsporum sp. (audounii, canis, gypseum, ferrugineum et al.)	0.01-4 MIC_{90}= 0.25-0.5
Pityriasis versicolor		*Malassezia* sp. *(furfur, globosa, obtuse, sympodialis etc).*	0.3-16 MIC_{90}= 0.125

INDICATIONS	INFECTING ORGANISM	MIC RANGE[1]
Systemic mycoses		
Candidiasis	*C. albicans*	0.008-8 MIC_{90}= 0.125
	C. parapsilosis	0.016-2 MIC_{90}= 0.25
	C. glabrata	0.008-16 MIC_{90}= 16
	C. krusei	0.008-8 MIC_{90}= 0.5
	C. tropicalis	0.03-8 MIC_{90}= 0.5
Aspergillosis	*A. fumigatus complex*	0.03-16 MIC_{90}= 0.5
	A. flavus complex	0.03-8 MIC_{90}= 0.5
	A. terreus complex	0.03-1 MIC_{90}= 0.25
	A. nidulans complex	0.03-8 MIC_{90}= 0.25
	A. niger complex	0.03-8 MIC_{90}= 0.5
Histoplasmosis	*H. capsulatum*	0.03-8 MIC_{90}= 0.06

When reviewing Table 21 above the following should be noted:

- All dermatophytes have the ability to cause infection of keratinaceous substrates like skin, hair, and nails. Species listed in this table are the most common for the clinical entity described (Rippon 1988; Elewski 1998).
- In general, dermatophytes are generally considered to be fully susceptible to itraconazole, resistant strains are very uncommon. However the MIC data presented is a composite of reports that may use different methodology; standardised CLSI methodology for testing antifungal susceptibility to dermatophytes only became available in 2008 (CLSI document M38-A2) (Fernandez-Torres, Carrillo et al. 2001; Sabatelli, Patel et al. 2006; Santos and Hamdan 2006).
- With regards to pityriasis veriscolor, seven species of Malassezia have now been recognised as causative agents. Antifungal susceptibility testing is difficult because they do not grow readily on the usual media. However, all are considered susceptible to itraconazole (Gueho, Midgley et al. 1996; Nakamura, Kano et al. 2000; Velegraki, Alexopoulos et al. 2004; Miranda, de Araujo et al. 2007).
- Several species of Candida may be aetiological agents, most commonly *C. albicans* (~48%), followed by *C. parapsilosis* (~19%), *C. glabrata* (~18%), *C. krusei* (~5%) and *C. tropicalis* (~5%). However, a number of other species may also be isolated (~5% eg *C. dubliensis*, *C. guilliermondii, C. lustianiae, C. kefry* etc). All are ubiquitous and occur naturally on humans. CLSI and EUCAST antifungal susceptibility methodology is available. Resistance to itraconazole (MIC >1 μg/ml) has been detected in most species; however, it occurs predominantly in isolates of *C. glabrata* (Espinel-Ingroff 2001; Pfaller, Messer et al. 2002; Hajjeh, Sofair et al. 2004 ; Richter, Galask et al. 2005; Chen, Slavin et al. 2006; Cuenca-Estrella, Gomez-Lopez et al. 2006; Pfaller and Diekema 2007; Ellis and Handke 2010).
- Overall, itraconazole resistance in *Aspergillus* remains low. The emergence of invasive infection due to triazole-resistant, including cross-resistant, *A. fumigatus* isolates is of increasing concern in Europe, where 3-6% of isolates have been reported resistant at different centres. However, to date, a similar emergence of triazole- and/or cross-resistant *A. fumigatus* has not been observed in the Australian setting. A recent surveillance study of all *A. fumigatus* isolates at The Alfred Hospital, Melbourne, identified no triazole-resistant *A. fumigatus* isolates over a one year period (May 2009 - April 2010) (Espinel-Ingroff 2001; Espinel-Ingroff, Boyle et al. 2001; Pfaller, Messer et al. 2002; Cuenca-Estrella, Gomez-Lopez et al. 2006; Sabatelli, Patel et al. 2006; Verweij, Mellado et al. 2007; Kidd, Handke et al. 2011) (S. Kidd, unpublished data).
- Itraconazole is an important antifungal for the management of histoplasmosis (Espinel-Ingroff 2001; Gonzalez, Fothergill et al. 2005; Sabatelli, Patel et al. 2006; Wheat, Freifeld et al. 2007)

If one assigns a clinical breakpoint and a target AUC/MIC ratio for optimal therapeutic effect then the minimum AUC required can be calculated. As highlighted in Table 21 above, these breakpoints and AUC/MIC ratios vary according to the infecting organism so it is instructive to consider multiple scenarios. For illustrative purposes, Table 22 below lists three scenarios selected based on the following rationale:

- A MIC90 of < 1 mcg/ml is appropriate for treating the majority of susceptible superficial and systemic infections within the proposed indications for this application
- A MIC90 of > 4 mcg/ml would normally be considered resistant but in some cases itraconazole is used to treat specific mycoses considered to be due to an organism resistant at this level if clinically indicated
- A MIC90 of 16 mcg/ml is the maximum point on the standard 0.0008-16 mcg/ml testing range employed in mycology laboratories.

A target AUC/MIC ratio of greater than 25 has been designated in Table 22 as it has been determined to be the ratio at which optimal efficacy rates are achieved for the triazole class (Andes 2003).

Table 22: Calculation of minimum AUC required for optimal therapeutic effect

Example number	Clinical breakpoint (mcg/ml)	Target AUC/MIC ratio	Minimum AUC required [1] (ng.hr/ml)
1	1	25	25
2	4	25	100
3	16	25	400

[1] Obtained by multiplying column 2 x column 3

In Figure 14 (below) the individual subject AUC_{inf} results were ranked in order of lowest to highest for both test and reference, with the minimum AUC thresholds arrived at in Table 22 above superimposed. This illustrates actual AUCs required for optimal therapeutic effect and compares the relative performance of **Lozanoc 50 mg hard capsules** and Sporanox® 100 mg Capsules in Study HGN007 (see pharmacokinetics section).

Figure 14: Study HGN 007 – Lozanoc 50 mg hard capsules (fed) vs Sporanox® 100 mg Capsules (fed); AUC/MIC ratio = 25

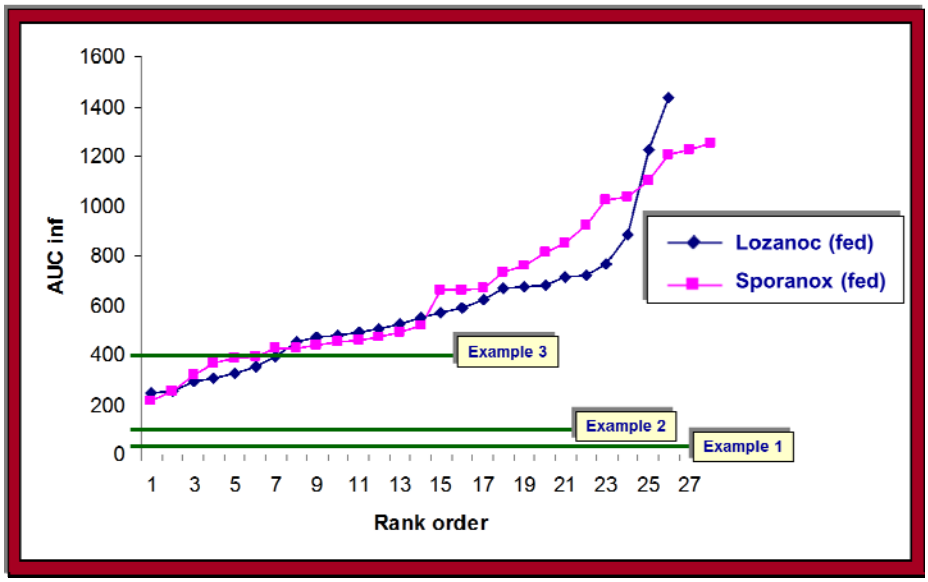


Figure 15 and Figure 16 (below) apply the same principles for each occurrence in Study HGN008:

Figure 15: Study HGN 008 first administration - Lozanoc 50 mg hard capsules (fed) vs Sporanox® 100 mg Capsules; AUC/MIC ratio = 25

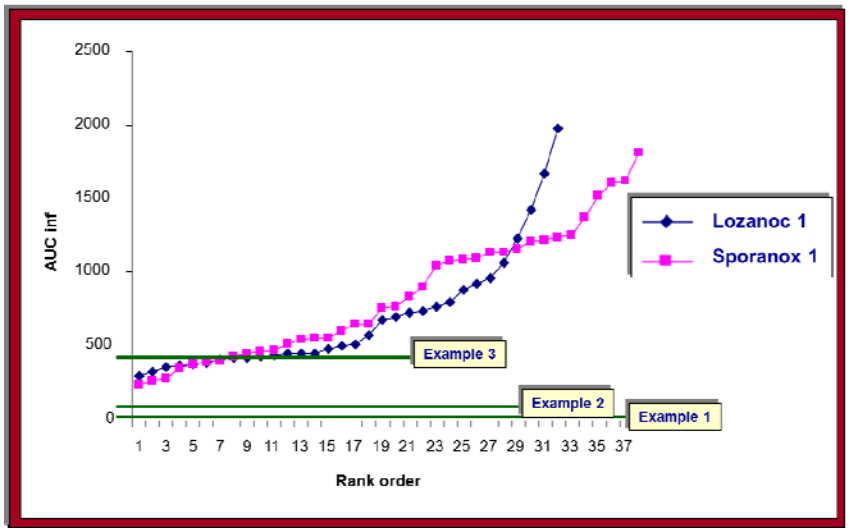
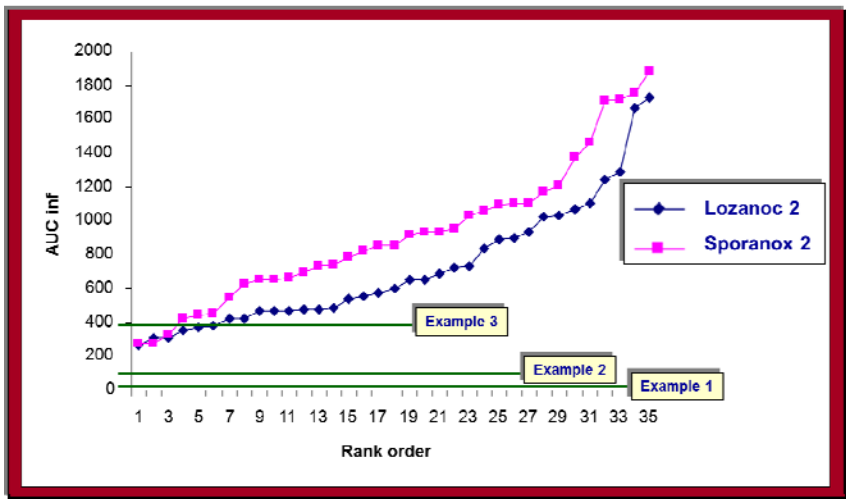


Figure 16: Study HGN 008 second administration - Lozanoc 50 mg hard capsules (fed) vs Sporanox® 100 mg Capsules; AUC/MIC ratio = 25



Review of Figure 15 and Figure 16 highlights that regardless of the formulation, all subjects in Study HGN007 and HGN008 achieved an exposure sufficient to achieve above the desired AUC/MIC ratio for Examples 1 and 2. As one might expect for oral itraconazole, the majority but not all subjects achieved an exposure sufficient to achieve above the desired AUC/MIC ratio for Example 3, with no apparent difference between the formulations.

The most important pharmacokinetic-pharmacodynamic (PK-PD) parameter for itraconazole is the AUC/MIC ratio which should be greater than 25 for optimal efficacy. The above data demonstrate that 50mg of the test product, taken in the **fed** state, achieves this comfortably for the above listed organisms and with more certainty compared to the highly variable Sporanox for MIC90 >4 mcg/ml and also for the majority when MIC >16 mcg/ml.

The effect of food on Lozanoc 50 mg hard capsules performance

A key question is whether Lozanoc 50 mg hard capsules should be taken in the fed or the fasted state, or whether it can be taken regardless of food. In terms of bioequivalence criteria based on geometric means, in Study HGN007 Lozanoc 50 mg Hard Capsules taken in the fed state performed better than in the fasted state. However, three observations suggest that Lozanoc 50 mg hard capsules can be taken regardless of food:

1. In Study HGN007, the variance in AUC(0-inf) for Lozanoc 50 mg hard capsules is significantly lower than Sporanox® 100 mg Capsules when the fed and fasted data are pooled, which in part is due to the variance being significantly less when Lozanoc 50 mg hard capsules are taken in the fasted state versus Sporanox® 100 mg Capsules in the fed state.
2. When one then compares the individual AUC/MIC ratios for subjects in Study HGN007: (i) taking Lozanoc 50 mg hard capsules in the fasted state versus Sporanox® 100 mg Capsules in the fed state (see Figure 17 below) and (ii) Lozanoc 50 mg Hard Capsules in the fasted state versus the fed state (see Figure 18 below), it is apparent that the performance of Lozanoc 50 mg hard capsules is comparable regardless of food.
3. In the onychomycosis efficacy study 70850702, Lozanoc 50 mg hard capsules was dosed in the fasted state (30 minutes prior to breakfast) and at week 24 demonstrated superior efficacy rates to placebo.

Figure 17: Study HGN 007 – Lozanoc 50 mg hard capsules (fasted) vs Sporanox® 100 mg Capsules (fed); AUC/MIC ratio = 25

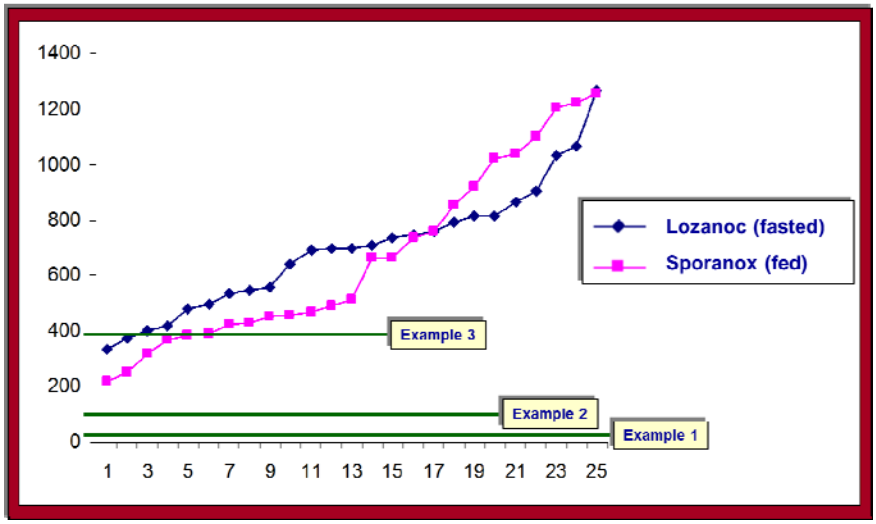
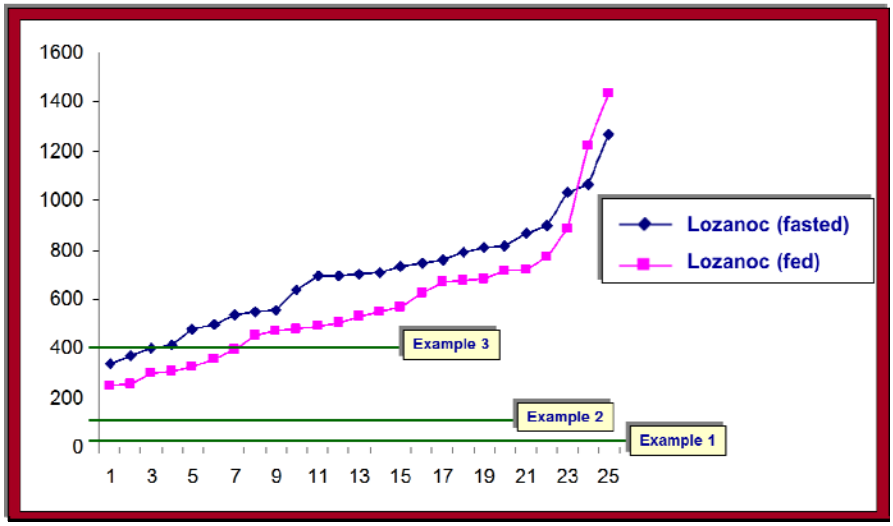


Figure 18: Study HGN 007 – Lozanoc 50 mg hard capsules fasted vs fed; AUC/MIC ratio = 25



The most important PK-PD parameter for itraconazole is the AUC/MIC ratio which should be greater than 25 for optimal efficacy. The above data demonstrate that 50mg of the test product, taken in **fasted** state, achieves this comfortably for the above listed organisms and with more certainty compared to the highly variable Sporanox for MIC90 >4 mcg/ml and also for the majority when MIC >16 mcg/ml.

Safety

No new or unexpected safety concerns were raised during the clinical studies.

Conclusion

As this application for Lozanoc 50 mg hard capsules has been submitted under Art 10(3), a so-called "hybrid" application, this allows the MAH to rely on some data from the innovator and, to supplement this with their own data (including bibliographic data). Sporanox is an established antifungal agent for the treatment of a wide variety of superficial and systemic fungal infections. It is widely used despite the known problems of high inter- and intra-individual variation. To get the "right" dose, frequent drug level monitoring may be required.

The test formulation under consideration has demonstrated advantages over the reference, such as lower inter and intra-individual variability, less pronounced food effect and therefore more predictability of dosing. In addition, the PK-PD parameter demonstrates that Lozanoc 50 mg hard capsules achieves the AUC/MIC ratio which should be greater than 25 for optimal efficacy in both the fed and fasted state for a number of organisms.

The clinical study in onychomycosis demonstrated superiority of Lozanoc 50 mg hard capsules compared to placebo. As the test and reference are not bioequivalent, they are not considered interchangeable. However Lozanoc 50 mg hard capsules can be considered a therapeutic alternative to Sporanox in the treatment of certain superficial and systemic mycoses (listed below). Therefore prescribing by brand name would be necessary.

In conclusion, it is considered that the application for Lozanoc 50 mg hard capsules is approvable for the proposed indication.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Overview

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, 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 notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan has been submitted for this product.

Conclusion

The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics of Lozanoc 50 mg hard capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of itraconazole are well-known, no additional data were required.

EFFICACY

With the exception of the bioequivalence studies and the onychomycosis clinical study, no new clinical data were submitted and none are required for this type of application.

The clinical study in onychomycosis demonstrated superiority of Lozanoc 50 mg hard capsules compared to placebo. As the test and reference are not bioequivalent, they are not considered interchangeable. However Lozanoc 50 mg hard capsules can be considered a therapeutic alternative to Sporanox in the treatment of certain superficial and systemic mycoses.

SAFETY

With the exception of the bioequivalence studies and the onychomycosis study, no new data were submitted and none are required for applications of this type. As the safety profile of itraconazole is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the studies.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with itraconazole is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome