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Assessment of comparative bioavailability of Itraconazole capsule 100mg in healthy subjects under fed conditions by using multiple bioequivalence approaches

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Abstract

Purpose: To evaluate the comparative oral bioavailability of Itraconazole capsule 100mg upon administering single dose to adult, healthy, human subjects in fed state by different bioequivalence approaches like average bioequivalence, population bioequivalence and individual bioequivalence and to monitor the safety of subjects upon administration of test and reference formulations.

Methods: An open label, balanced, randomized, two-treatment, two-sequence, four-period (fully replicated), crossover, single dose comparative oral bioavailability study was conducted in 16 healthy, adult, human subjects in fed state. Test product, Itraconazole capsule 100mg and reference product, SPORANOX® (Itraconazole) capsule 100mg were administered in fed state.

Findings: The test product, Itraconazole capsule 100mg showed bioequivalence against reference product, SPORANOX® (Itraconazole) capsule 100mg in healthy subjects under fed state. Also, the test product exhibited similar safety and tolerability profile compared to reference product. There were no reports of serious adverse events and deaths in the course of study conduct.

Conclusions: The test product was found to be bioequivalent to reference product in healthy human subjects under fed state by evaluating different bioequivalence approaches like average bioequivalence, population bioequivalence and individual bioequivalence.

Key words: Itraconazole, average bioequivalence, population bioequivalence and individual bioequivalence, fed study

INTRODUCTION

Itraconazole is an azole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature (1, 2, 3):

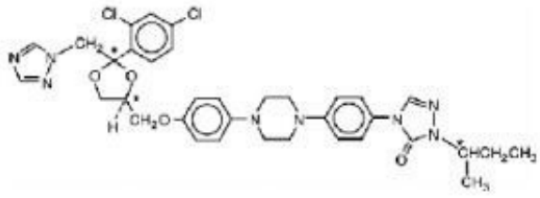

Figure 1: Chemical structure of Itraconazole

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1 ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H 1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4 triazolin-5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1 ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of $C_{35}H_{38}C_{l2}N_{8O4}$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1 (1, 2, 3).

SPORANOX® capsule contain 100 mg of itraconazole coated on sugar spheres (composed of sucrose, maize starch, and purified water). Inactive ingredients are hard gelatin capsule, hypromellose, polyethylene glycol (PEG) 20,000, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22 and D&C Red No. 28. As test itraconazole 100mg capsule, Strides Arcolab Limited, India if a generic version of SPORANOX®, USA, test product is qualitatively and quantitatively similar to the standard drug.

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. The observed absolute oral bioavailability of itraconazole is about 55%. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with Cmax values of 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 b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing ((1, 2, 3).

Itraconazole capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Vulvovaginal candidosis.
2. Pityriasis versicolor.
3. Dermatophytoses caused by organisms susceptible to itraconazole (Trichophyton spp., Microsporum spp., Epidermophyton floccosum) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum.
4. Oropharyngeal candidosis.
5. Onychomycosis caused by dermatophytes and/or yeasts.
6. The treatment of histoplasmosis.
7. Sporanox is indicated in the following systemic fungal conditions when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity.
   - Treatment of aspergillosis and candidosis
   - Treatment of cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system.
   - Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection.

Sporanox is also indicated in the prevention of fungal infection during prolonged neutropenia when standard therapy is considered inappropriate.

This study was executed to understand the test product, Itraconazole capsule 100mg in-vivo behavior against the standard drug SPORANOX® (Itraconazole) capsule 100mg. This was a pilot study and not planned for any regulatory submission purpose. This study was planned as per the draft product specific guidance from USFDA (4). As it was an exploratory study, only parent analyte was quantified.

Thus, the purpose of the current study was to evaluate the comparative oral bioavailability of newly established Itraconazole capsule 100mg (Strides Arcolab Limited, India) with that of the standard drug SPORANOX® (Itraconazole) capsule 100mg upon administering single dose to adult, healthy, human subjects under fed state by different bioequivalence approaches like average bioequivalence, population bioequivalence and individual bioequivalence and to monitor the safety of subjects upon administration of test and reference formulations.

MATERIALS AND METHODS

Ethical considerations

The study was commenced only after obtaining an approval for the study protocol from the Institutional ethics committee and written informed consent from each subject. The study procedure was explained to the subjects in their respective native languages. The study was conducted as per the Good Clinical Practices, Declaration of Helsinki, and applicable requirements of principles of Good Laboratory Practices (5,6,7).

Study design

This was an open label, randomized, balanced, single-dose, two-treatment, two-sequence, four-period, crossover comparative oral bioavailability study. As it's a fully replicated design study, all the study subjects were administered the test product in two periods and the reference product in the other two periods as per the assigned randomization schedule. The study subjects were randomly assigned to receive test or reference products in fed state. Randomization was carried out using SAS® Version 9.2 (SAS Institute Inc., USA). Randomization was done in blocks using PROC PLAN such that the design was balanced. A washout period of at least 10 days was adhered between each period in the study.

Study procedure

All subjects were housed in the clinic from at least 11 hours before dosing to at least 24 hours post dose. The subjects were reported to clinic for 48.0, 72.0, 96.0 and 120.0 hours post dose ambulatory sample collection. Fasting was observed for at least 10 hours before serving high fat high-calorie breakfast. 30 minutes after serving high fat high-calorie breakfast, the subjects were dosed with 240mL of water in an ambient temperature. Fasting was observed for at least 04 hours post-dose. Water in-take was restricted (at least) from 1 hour before dosing until 2 hours post dosing (except for water used for drug administration). The subjects remained seated for 4 hours post-dose and only necessary movement was allowed during this period. There after subjects were allowed to ambulate freely during the remainder of the study. Subjects were instructed not to take any prescription medications within 14days prior to dosing and throughout the study. Subjects were instructed not to take any over the counter (OTC) products, herbal medications, etc within 7 days prior to dosing and throughout the study.

One capsule of either the test product or the reference product was administered at 0.0 hour to the subjects in sitting posture with 240mL of water at ambient temperature in each period under the supervision of trained study personnel. This activity was followed by mouth check to assess compliance to dosing.,

In each period, total of 22 venous blood samples were collected at 0.0 (pre-dose), 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0 and 120.0 hours post dose in labeled K_3 EDTA vacutainers for the evaluation of pharmacokinetic parameters. Pre-dose sample was collected within 1 hour before drug administration. After collection of blood samples from all subjects at each time point, they were centrifuged at 3000rpm for 15 minutes at 4°C to separate the plasma. After separation of plasma, they were transferred in labelled tubes in duplicated and stored in a deep freezer at -20º± 10ºC at the clinical site until shipment to the bioanalytical laboratories.

Study population

Healthy subjects of age between 18 and 45 years (both inclusive) and having a BMI between 18.5 and 24.9 weight in kg/ height^2 in meter were selected on the basis of laboratory evaluations during screening, medical history, clinical

examination, Chest X-ray (P/A view) and ECG recordings. For the reason of numerous socio-cultural circumstances, female subject could not be convinced to stay at the clinical facility. Also, generally females in country like India are likely to have lesser hemoglobin levels. Further, the drug under investigation is not recognized to have gender specific pharmacokinetic profile. Therefore, the study was conducted by enrolling male subjects.

Key exclusion criteria included hypersensitivity to Itraconazole or other related class of drugs, history or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological, ophthalmic or psychiatric disease or disorder, history of light sensitive diseases (e.g. lupus erythematosus, porphyria cutanea tarda, erythropoitic protoporphyria, variegate porphyria, xeroderma pigmentosum and albinism), any treatment which could bring about induction or inhibition of hepatic microsomal enzyme system within one month of the study starting, history or presence of significant alcoholism or drug abuse in the past one year, history or presence of significant smoking and presence of any other major illness. Smokers, who smoke more than or equal to 10 cigarettes per day or more than or equal to 20 biddies per day were excluded from the study.

This study was conducted according to requirements of applicable ICMR guidelines, Good Clinical Practices for Clinical Research in India - Amended version 2005, ICH (Step 5) "Guidance on Good Clinical Practice", Declaration of Helsinki (Seoul, October 2008), related USFDA guidelines and all applicable requirements of Principles of Good Laboratory Practices (OECD and Schedule L-1 of D & C Rule 1945) (8-11).

The study protocol and informed consent documents were submitted for Independent Ethics Committee (IEC) review and approval. Subjects were enrolled into the study only upon receipt of IEC approval.

Safety

Safety and tolerability of test and reference product for the enrolled subjects were assessed throughout the study by monitoring adverse events (AEs), standard clinical laboratory tests (clinical biochemistry, urinalysis, and hematology), physical examinations, vital signs, and 12-lead electrocardiograms (ECGs). Post-study safety follow-up was also carried out.

Bioanalytic methods

The plasma samples were assayed by validated method developed at Jeevan Scientific Technology Limited, Hyderabad, which was specific for the determination of Itraconazole. A validated HPLC-MS/MS bioanalytical method developed for the quantification of Itraconazole in plasma was employed for subject's sample analysis. The bioanalytical method was validated as per the recommendation from FDA (12).

Pharmacokinetic analysis

The below mentioned pharmacokinetic parameters were calculated for Itraconazole from the time and concentration data using a non-compartmental analysis by using WinNonlin® professional software (Version 5.3, Pharsight Corporation, USA)

C_{max}:	Peak plasma concentration
AUC_{0-t}:	The area under the plasma concentration versus time curve from zero to last sample collection
$AUC_{0-\infty}$:	The area under the plasma concentration versus time curve from zero to infinity
$AUC_{0-t}/AUC_{0-\infty}$:	% AUC extrapolated area
T_{max}:	The time to maximum plasma concentration
K_{el}:	The terminal elimination rate constant
$t_{½}$:	The half-life

Statistical analysis

Descriptive statistics was computed for each pharmacokinetic parameter for the test and reference product of Itraconazole. Intra-subject variability of reference product, termed as S_{WR}, was evaluated using PROC GLM in SAS® for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The within subject standard deviation for reference product was derived by PROC GLM in SAS® Software, Version 9.2, using sequence as fixed effect in ANOVA model.

Statistical analysis of primary pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Itraconazole was carried out by using average bioequivalence, population bioequivalence and individual bioequivalence approaches.

RESULTS

Study subjects' demographic characteristics

A total of 14 study subjects were enrolled into the study and their demographic characteristics were comparable and presented in Table 1.

Table 1: Demographic characteristics of study subjects

Demographic characteristics	Mean	Min.	Max.
Height (centimeter)	164.9	157	174
Weight (kilograms)	60.7	50	75
BMI (kilograms / meters ^{2})	22.3	18.81	24.83
Age (years)	27.6	20	35

BMI = body mass index
Min. = Minimum
Max. = Maximum

Pharmacokinetic and bioequivalence assessment

Mean plasma concentrations of Itraconazole following single 100mg dose of test product, Itraconazole capsule 100mg and the standard drug SPORANOX® (Itraconazole) capsule 100mg concentrations in fed state are presented in figure 2.

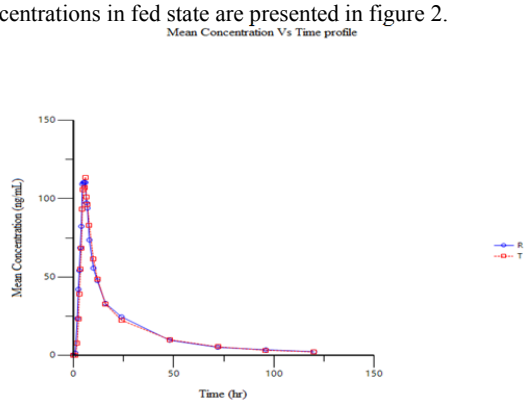

Figure 2: Mean plasma drug concentration–time curve for 100mg mg of test Itraconazole capsule 100mg Vs standard drug SPORANOX® (Itraconazole) capsule 100mg in fed state

The pharmacokinetic parameters of Itraconazole following single 100mg dose of test Itraconazole capsule 100mg and the standard drug SPORANOX® (Itraconazole) capsule 100mg concentrations in fed state are presented in Table 2.

Table 2: Pharmacokinetic parameters of Itraconazole in 14 study subjects in fed state

PK parameters (Arithmetic mean ± SD)	Itraconazole capsule 100mg (T1)	Itraconazole capsule 100mg (T2)
C_{max} (ng/mL)	108.63 ± 31.63	145.42 ± 80.41
AUC_{0-t} (ng h/mL)	1575.94 ± 574.21	2147.17 ± 1529.72
$AUC_{0-\infty}$ (ng h/mL)	1676.45 ± 689.90	2285.87 ± 1696.84
T_{max} (h)	5.75 (3.50 – 7.00)	5.50 (4.00 – 6.50)
Kel	0.03 ± 0.01	0.03 ± 0.01
t½ (h)	30.93 ± 15.06	29.38 ± 11.49

PK parameters (Arithmetic mean ± SD)	SPORANOX® (Itraconazole) capsule 100mg (R1)	SPORANOX® (Itraconazole) capsule 100mg (R2)
C_{max} (ng/mL)	143.35 ± 83.77	127.90 ± 60.84
AUC_{0-t} (ng h/mL)	1995.88 ± 1205.81	1830.96 ± 1128.74
$AUC_{0-\infty}$ (ng h/mL)	2107.53 ± 1352.60	1938.49 ± 1213.28
T_{max} (h)	5.00 (3.50 – 6.50)	5.50 (3.00 – 7.00)
Kel	0.03 ± 0.008	0.03 ± 0.01
t½ (h)	26.29 ± 9.96	28.43 ± 11.95

The bioequivalence summary data of Itraconazole, following single 100mg dose of test product, Itraconazole capsule 100mg and the standard drug SPORANOX® (Itraconazole) capsule 100mg concentrations in fed state are presented in Table 3.

Table 3: Bioequivalence summary by applying ABE, PBE, and IBE approaches

ABE evaluation variances	Test/reference values for log-transformed	90% Confidence interval
C_{max} (ng/mL)	95.36	82.41 – 110.35
AUC_{0-t} (ng h/mL)	98.70	84.66 – 115.06
$AUC_{0-\infty}$ (ng h/mL)	99.26	85.18 – 115.67
	Pass or fail ABE	✓

PBE evaluation variances	Linearized point estimate	95% upper confidence bound
C_{max} (ng/mL)	95.36	- 0.227 (Reference scale)
AUC_{0-t} (ng h/mL)	98.70	- 0.317 (Reference scale)
$AUC_{0-\infty}$ (ng h/mL)	99.26	- 0.328 (Reference scale)
	Pass or fail PBE	✓

IBE evaluation variances	Linearized point estimate	95% upper confidence bound
C_{max} (ng/mL)	95.36	-0.110 (Reference scale)
AUC_{0-t} (ng h/mL)	98.70	-0.109 (Reference scale)
$AUC_{0-\infty}$ (ng h/mL)	99.26	-0.100 (Reference scale)
	Pass or fail IBE	✓

Note: ABE: Average bioequivalence; IBE: Individual bioequivalence; PBE: Population bioequivalence

Safety and tolerability profile

In total, 14 subjects received the investigational drugs in all the periods. Both the test and reference products were well tolerated. There were no deaths reported during the study. The safety profile of test Itraconazole capsule 100mg was found comparable to the standard drug SPORANOX® (Itraconazole) capsule 100mg in fed state.

DISCUSSION

Though there has been a significant improvement in pharmaceutical research, the change is inevitable. Generic drugs play a significant role in treating the patients all across the globe. The significant advantages of generic drugs are lower cost and providing same efficacy as innovator product. ABE approach is the gold standard bioequivalence evaluation method. Whether the drug belongs to a highly variable drug category or a narrow therapeutic index drug category, same ABE approach is used for the evaluation and confidence limit is adjusted to make sure that the particular category of drug is evaluated as applicable. If the drug of interest for the evaluation is a highly variable drug category, 90% confidence internal will be applied and the confidence limit will be widened. If the drug of interest for the evaluation is a narrow therapeutic index drug category, 90% confidence internal will

be applied and the confidence limit will be tightened. Though there have been numerous changes in the usage of ABE approach, there were many discussions and doubts about using this approach for narrow therapeutic index drug category and highly variable drug category. Then the alternative approaches like PBE and IBE approaches emerge (13-17).

From the available literatures, it is very well established that Itraconazole has a high intra-subject variability. Due to its high intra-subject variability, the available studies were conducted by partial/ complete replicate design (18-22).

This study was undertaken to evaluate the comparative oral bioavailability of test Itraconazole capsule 100mg against the standard drug SPORANOX® (Itraconazole) capsule 100mg in fed state. In this study, the study outcomes were assessed by ABE approach along with PBE and IBE approaches. From the mean plasma concentration of test Itraconazole capsule 100mg, it was found to be comparable to the standard drug SPORANOX® (Itraconazole) capsule 100mg. Form the mean plasma drug concentration, it is quite evident that the test product drug release was comparable to the reference product and the same was observed with the pharmacokinetic parameters also. From the bioequivalence summary data, it is very clear that the test product is bioequivalent to the reference product. All the bioequivalence approaches assessment shown the same outcome. From ABE assessment, it was concluded that all the parameters (Cmax, AUC_{0-t} and $AUC_{0-\infty}$) were met the bioequivalence criteria and same is the case with PBE and IBE approaches also. (13).

There were no deaths and serious adverse events reported during the conduct of the study. Both the test and reference formulation exhibited comparable safety and tolerability profiles.

CONCLUSIONS

Based on the outcome of this study by a conventional bioequivalence approach (ABE approach), it was concluded that the test product, Itraconazole capsule 100mg was found to be comparable (bioequivalent) to the standard drug, SPORANOX® (Itraconazole) capsule 100mg. The same study outcome was seen with the other bioequivalence approaches (PBE and IBE approaches) as well. This study provides an alternative approach to establish BE between the test and reference formulations containing drugs with high within subject variability by using different BE approaches (PBE and IBE approaches). Certainly the study outcomes indicate that when assessing drugs with similar characteristics (high within subject variability), PBE and IBE approaches may be applied to overcome the inadequacies of conventional BE approach (ABE approach).

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Compliance with ethical standards

Funding

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Ethical approval

The study was approved by Samkshema independent ethics committee. The principles outlined in the declaration of Helsinki were adhered to while performing the study.

Informed consent

Informed consent was obtained separately from all study subjects enrolled in the study.

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