ITRACONAZOLE - itraconazole solution
Camber Pharmaceuticals, Inc.

Itraconazole Oral Solution

BOXED WARNING

Congestive Heart Failure, Cardiac Effects and Drug Interactions

<u>Congestive Heart Failure and Cardiac Effects:</u>

• If signs or symptoms of congestive heart failure occur during administration of itraconazole oral solution, continued itraconazole oral solution use should be reassessed.

• When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations for more information.)

<u>Drug Interactions:</u>

• Coadministration of a number of CYP3A4 substrates are contraindicated with itraconazole oral solution. Some examples of drugs that are contraindicated for coadministration with itraconazole oral solution are: methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazole, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor, finerenone, voclosporin.

• Coadministration with colchicine, fesoterodine and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment.

• Coadministration with eliglustat is contraindicated in subjects that are poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors.

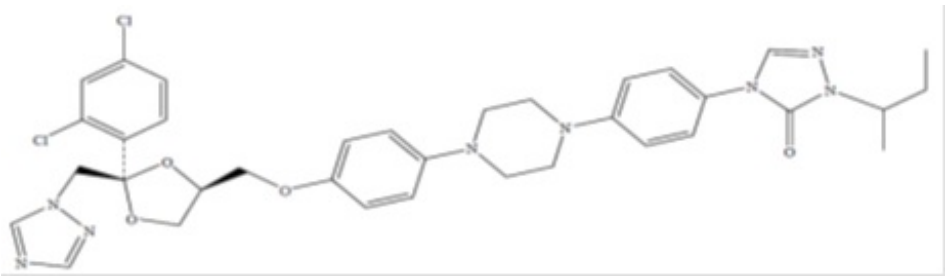
• Coadministration with venetoclax is contraindicated in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) during the dose initiation and ramp-up phase of venetoclax. See PRECAUTIONS: Drug Interactions Section for specific examples.

• Coadministration with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. See CONTRAINDICATIONS and WARNINGS Sections, and PRECAUTIONS: Drug Interactions Section for specific examples.

DESCRIPTION

Itraconazole, 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-sec-Butyl-4-[p-[4-[p-[[2R *,4S *)-2-(2,4-dichloro phenyl)-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
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-methyl propyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.63. It is a white or almost white powder. It is freely soluble in methylene chloride, sparingly soluble in tetrahydrofuran, very slightly soluble in alcohol, practically insoluble in water. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/ aq. Buffer of pH: 8.1) partition coefficient of 5.66 at pH 8.1.
Itraconazole oral solution contains 10 mg of itraconazole USP per mL, solubilized by hydroxypropyl-β-cyclodextrin (400 mg/mL) as a molecular inclusion complex.

Itraconazole oral solution is clear, colorless to yellowish brown liquid with a target pH of 2. Other ingredients are ascorbic acid, hydrochloric acid, propylene glycol, purified water, non crystallizing sorbitol solution, saccharin sodium, sodium hydroxide, ART Cherry flavor.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism:

Itraconazole

General Pharmacokinetic Characteristics

Peak plasma concentrations are reached within 2.5 hours following administration of the oral solution. 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 C_{max} and AUC values 4 to 7-fold higher than those seen after a single dose. Steady-state C_{max} values of about 2 mcg/mL are reached after oral administration of 200 mg once daily. 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. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 mL/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption

Itraconazole is rapidly absorbed after administration of the oral solution. Peak plasma concentrations of itraconazole are reached within 2.5 hours following administration of the oral solution under fasting conditions. The observed absolute bioavailability of itraconazole under fed conditions is about 55% and increases by 30% when the oral solution is taken in fasting conditions. Itraconazole exposure is greater with the oral solution than with the capsule formulation when the same dose of drug is given. (see WARNINGS)

Distribution

Most of the itraconazole in plasma is bound to protein (99.8%), with albumin being the main binding component (99.6% for the hydroxy-metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (>700 L), suggesting extensive distribution into tissues. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma.

Metabolism

Itraconazole is extensively metabolized by the liver into a large number of metabolites. *In vitro* studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole; trough plasma concentrations of this metabolite are about twice those of itraconazole.

Excretion
Itraconazole is excreted mainly as inactive metabolites in urine (35%) and in feces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabeled dose, fecal excretion of unchanged drug ranges from 3% to 18% of the dose.

Special Populations:

Renal Impairment:

Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200 mg oral dose of itraconazole was conducted in three groups of patients with renal impairment (uremia: n = 7; hemodialysis: n = 7; and continuous ambulatory peritoneal dialysis: n = 5). In uremic subjects with a mean creatinine clearance of 13 mL/min.×1.73 m^2, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and $AUC_{0\ to\ 8h}$). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50 to 79 mL/min), moderate (defined in this study as CrCl 20 to 49 mL/min), and severe renal impairment (defined in this study as CrCl <20 mL/min) were similar to that in healthy subjects (range of means 42 to 49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively). Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Hepatic Impairment:

Itraconazole is predominantly metabolized in the liver. A pharmacokinetic study was conducted in 6 healthy and 12 cirrhotic subjects who were administered a single 100 mg dose of itraconazole as capsule. A statistically significant reduction in mean C_{max}(47%) and a two fold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC, was similar in cirrhotic patients and in healthy subjects. Data are not available in cirrhotic patients during long-term use of itraconazole. (See CONTRAINDICATIONS, PRECAUTIONS: Drug Interactions and DOSAGE AND ADMINISTRATION.)

Decreased Cardiac Contractility:

When itraconazole was administered intravenously to anesthetized dogs, a dose-related

negative inotropic effect was documented. In a healthy volunteer study of itraconazole intravenous infusion, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of itraconazole oral solution, monitor carefully and consider other treatment alternatives which may include discontinuation of itraconazole oral solution administration. (See BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Cystic Fibrosis:
Seventeen cystic fibrosis patients, ages 7 to 28 years old, were administered itraconazole oral solution 2.5 mg/kg b.i.d. for 14 days in a pharmacokinetic study. Sixteen patients completed the study. Steady state trough concentrations >250 ng/mL were achieved in 6 out of 11 patients ≥16 years of age but in none of the 5 patients <16 years of age. Large variability was observed in the pharmacokinetic data (%CV for trough concentrations = 98% and 70% for ≥16 and <16 years, respectively; %CV for AUC = 75% and 58% for ≥16 and <16 years, respectively). If a patient with cystic fibrosis does not respond to itraconazole oral solution, consideration should be given to switching to alternative therapy.

Hydroxypropyl-ß-Cyclodextrin:
The oral bioavailability of hydroxypropyl-β-cyclodextrin given as a solubilizer of itraconazole in oral solution is on average lower than 0.5% and is similar to that of hydroxypropyl-β-cyclodextrin alone. This low oral bioavailability of hydroxypropyl-β-cyclodextrin is not modified by the presence of food and is similar after single and repeated administrations.

MICROBIOLOGY

Mechanism of Action:
*In vitro*studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.
Antimicrobial Activity:
Itraconazole has been shown to be active against most strains of the following microorganism,

both *in vitro*and in clinical infections.
Candida albicans
Susceptibility Testing Methods:
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.
Drug Resistance:
Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro*and from patients receiving prolonged therapy.

Candida krusei, Candida glabrata and *Candida tropicalis* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole *in vitro*.
Itraconazole is not active against *Zygomycetes* (e.g., *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

Cross-Resistance:

In systemic candidosis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of itraconazole therapy.
Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed.
Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

CLINICAL STUDIES

Oropharyngeal Candidiasis:

Two randomized, controlled studies for the treatment of oropharyngeal candidiasis have been conducted (total n = 344). In one trial, clinical response to either 7 or 14 days of itraconazole oral solution, 200 mg/day, was similar to fluconazole tablets and averaged 84% across all arms. Clinical response in this study was defined as cured or improved (only minimal signs and symptoms with no visible lesions). Approximately 5% of subjects were lost to follow-up before any evaluations could be performed. Response to 14 days therapy of itraconazole oral solution was associated with a lower relapse rate than 7 days of itraconazole therapy. In another trial, the clinical response rate (defined as cured or improved) for itraconazole oral solution was similar to clotrimazole troches and averaged approximately 71% across both arms, with approximately 3% of subjects lost to follow-up before any evaluations could be performed. Ninety-two percent of the patients in these studies were HIV seropositive.
In an uncontrolled, open-label study of selected patients clinically unresponsive to fluconazole tablets (n = 74, all patients HIV seropositive), patients were treated with itraconazole oral solution 100 mg b.i.d. (Clinically unresponsive to fluconazole in this study was defined as having received a dose of fluconazole tablets at least 200 mg/day for a minimum of 14 days.) Treatment duration was 14 to 28 days based on response. Approximately 55% of patients had complete resolution of oral lesions. Of patients who responded and then entered a follow-up phase (n = 22), all relapsed within 1 month (median 14 days) when treatment was discontinued. Although baseline endoscopies had not been performed, several patients in this study developed symptoms of esophageal candidiasis while receiving therapy with itraconazole oral solution. Itraconazole oral solution has not been directly compared to other agents in a controlled trial of similar patients.

Esophageal Candidiasis:
A double-blind randomized study (n = 119, 111 of whom were HIV seropositive) compared itraconazole oral solution (100 mg/day) to fluconazole tablets (100 mg/day). The dose of each was increased to 200 mg/day for patients not responding initially. Treatment continued for 2 weeks following resolution of symptoms, for a total duration of treatment of 3 to 8 weeks. Clinical response (a global assessment of cured or improved) was not significantly different between the two study arms, and averaged approximately 86% with 8% lost to follow-up. Six of 53 (11%) itraconazole-treated patients and 12/57 (21%) fluconazole-treated patients were escalated to the 200 mg dose in this trial. Of the subgroup of patients who responded and entered a follow-up phase (n = 88), approximately 23% relapsed across both arms within 4 weeks.

INDICATIONS AND USAGE

Itraconazole oral solution is indicated for the treatment of oropharyngeal and esophageal candidiasis.
(See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

CONTRAINDICATIONS

Congestive Heart Failure:
Itraconazole oral solution should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections. (See BOXED WARNING, WARNINGS, PRECAUTIONS: Drug Interactions-Calcium Channel Blockers, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations.)
Drug Interactions:
Coadministration of a number of CYP3A4 substrates are contraindicated with itraconazole. Some examples of drugs for which plasma concentrations increase are: methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazole, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor, finerenone, voclosporin. In addition, coadministration with colchicine, fesoterodine, and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment, and coadministration with eliglustat is contraindicated in subjects that are poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors. (See PRECAUTIONS: Drug Interactions Section for specific examples.) This increase in drug concentrations caused by coadministration with itraconazole may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade

de pointes, a potentially fatal arrhythmia. Some specific examples are listed in PRECAUTIONS: Drug Interactions.

Coadministration with venetoclax is contraindicated in patients with CLL/SLL during the dose initiation and ramp-up phase of venetoclax due to the potential for an increased risk of tumor lysis syndrome.

Itraconazole is contraindicated for patients who have shown hypersensitivity to itraconazole. There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing itraconazole to patients with hypersensitivity to other azoles.

WARNINGS

Hepatic Effects:

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition, and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued itraconazole use or reinstitution of treatment with itraconazole is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)

Cardiac Dysrhythmias:

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as cisapride, pimozide, methadone, or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole oral solution is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Cardiac Disease:

Itraconazole oral solution should not be used in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk. For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of itraconazole therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole oral solution, monitor carefully and consider other treatment alternatives which may include discontinuation of itraconazole oral solution administration.

Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole intravenous infusion, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours

later.
Itraconazole oral solution has been associated with reports of congestive heart failure. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg although there were also cases reported among those receiving lower total daily doses.
Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of itraconazole and felodipine or nisoldipine is contraindicated.
Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CONTRAINDICATIONS, CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS: Drug Interactions, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Interaction Potential:

Itraconazole has a potential for clinically important drug interactions. Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in PRECAUTIONS: Drug Interactions.

Interchangeability:

Itraconazole oral solution and itraconazole capsules should not be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. Only itraconazole oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

Hydroxypropyl-β-cyclodextrin:

Itraconazole oral solution contains the excipient hydroxypropyl-β-cyclodextrin which produced adenocarcinomas in the large intestine and exocrine pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these adenocarcinomas is unknown. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Treatment of Severely Neutropenic Patients:

Itraconazole oral solution as treatment for oropharyngeal and/or esophageal candidiasis was not investigated in severely neutropenic patients. Due to its pharmacokinetic properties, itraconazole oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

PRECAUTIONS

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a

serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. The risks and benefits of itraconazole use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: Hepatotoxicity and Information for Patients.)

Adverse Events Reported in Oropharyngeal or Esophageal Candidiasis Trials

U.S. adverse experience data are derived from 350 immunocompromised patients (332 HIV seropositive/AIDS) treated for oropharyngeal or esophageal candidiasis. Table 3 below lists adverse events reported by at least 2% of patients treated with itraconazole oral solution in U.S. clinical trials. Data on patients receiving comparator agents in these trials are included for comparison.

Table 3: Summary of Adverse Events Reported by ≥2% of Itraconazole Treated Patients in U.S. Clinical Trials (Total)

Body System/ Adverse Event	Itraconazole			
	Total (n = 350*) %	**All controlled studies (n = 272) %**	**Fluconazole (n = 125 †) %**	**Clotrimazole (n = 81 ‡) %**
Gastrointestinal disorders				
Nausea	11	10	11	5
Diarrhea	11	10	10	4
Vomiting	7	6	8	1
Abdominal pain	6	4	7	7
Constipation	2	2	1	0
Body as a whole				
Fever	7	6	8	5
Chest pain	3	3	2	0
Pain	2	2	4	0
Fatigue	2	1	2	0
Respiratory disorders				
Coughing	4	4	10	0
Dyspnea	2	3	5	1
Pneumonia	2	2	0	0
Sinusitis	2	2	4	0
Sputum increased	2	3	3	1
Skin and appendages disorders				
Rash				
Increased sweating	4	5	4	6
	3	4	6	1

Skin disorder unspecified	2	2	2	1
Central/peripheral nervous system				
Headache Dizziness	4 2	4 2	6 4	6 1
Resistance mechanism disorders				
Pneumocystis carinii infection	2	2	2	0
Psychiatric disorders				
Depression	2	1	0	1

*Of the 350 patients, 209 were treated for oropharyngeal candidiasis in controlled studies, 63 were treated for esophageal candidiasis in controlled studies and 78 were treated for oropharyngeal candidiasis in an open study.

† Of the 125 patients, 62 were treated for oropharyngeal candidiasis and 63 were treated for esophageal candidiasis.

‡All 81 patients were treated for oropharyngeal candidiasis.

Adverse events reported by less than 2% of patients in U.S. clinical trials with itraconazole included: adrenal insufficiency, asthenia, back pain, dehydration, dyspepsia, dysphagia, flatulence, gynecomastia, hematuria, hemorrhoids, hot flushes, implantation complication, infection unspecified, injury, insomnia, male breast pain, myalgia, pharyngitis, pruritus, rhinitis, rigors, stomatitis ulcerative, taste perversion, tinnitus, upper respiratory tract infection, vision abnormal, and weight decrease. Edema, hypokalemia and menstrual disorders have been reported in clinical trials with itraconazole capsules.

Adverse Events Reported from Other Clinical Trials

A comparative clinical trial in patients who received intravenous itraconazole followed by itraconazole oral solution or received Amphotericin B reported the following adverse events in the itraconazole intravenous/itraconazole oral solution treatment arm which are not listed above in the subsection “Adverse Events Reported in Oropharnyngeal or Esophageal Candidiasis Trials” or listed below as post-marketing reports of adverse drug reactions: serum creatinine increased, blood urea nitrogen increased, renal function abnormal, hypocalcemia, hypomagnesemia, hypophosphatemia, hypotension, tachycardia and pulmonary infiltration.
In addition, the following adverse drug reactions were reported in patients who participated in itraconazole oral solution clinical trials:

*Cardiac Disorders:*cardiac failure;

*General Disorders and Administration Site Conditions:*edema;
*Hepatobiliary Disorders:*hepatic failure, hyperbilirubinemia;

*Metabolism and Nutrition Disorders:*hypokalemia;
*Reproductive System and Breast Disorders:*menstrual disorder
The following is a list of additional adverse drug reactions associated with itraconazole that have been reported in clinical trials of itraconazole capsules and itraconazole IV excluding the adverse reaction term “Injection site inflammation” which is specific to the injection route of administration:
*Cardiac Disorders:*left ventricular failure;
*Gastrointestinal Disorders:*gastrointestinal disorder;
*General Disorders and Administration Site Conditions:*face edema;
*Hepatobiliary Disorders:*jaundice, hepatic function abnormal;
*Investigations:*alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, urine analysis abnormal;
*Metabolism and Nutrition Disorders:*hyperglycemia, hyperkalemia;
*Nervous System Disorders:*somnolence;
*Psychiatric Disorders:*confusional state;
*Renal and Urinary Disorders:*renal impairment;
*Respiratory, Thoracic and Mediastinal Disorders:*dysphonia;
*Skin and Subcutaneous Tissue Disorders:*rash erythematous;
*Vascular Disorders:*hypertension
In addition, the following adverse drug reaction was reported in children only who participated in itraconazole oral solution clinical trials: mucosal inflammation.

Post-marketing Experience

Adverse drug reactions that have been first identified during post-marketing experience with itraconazole (all formulations) are listed in Table 4 below. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 4: Post-marketing Reports of Adverse Drug Reactions

Blood and Lymphatic System Disorders:	Leukopenia, neutropenia, thrombocytopenia
Immune System Disorders:	Anaphylaxis; anaphylactic, anaphylactoid and allergic reactions; serum sickness; angioneurotic edema
Metabolism and Nutrition Disorders:	Hypertriglyceridemia
Nervous System Disorders:	Peripheral neuropathy, paresthesia, hypoesthesia, tremor
Eye Disorders:	Visual disturbances, including vision blurred and diplopia
Ear and Labyrinth Disorders:	Transient or permanent hearing loss

Cardiac Disorders:	Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders:	Pulmonary edema
Gastrointestinal Disorders:	Pancreatitis
Hepatobiliary Disorders:	Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes
Skin and Subcutaneous Tissue Disorders:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, alopecia, photosensitivity, urticaria
Musculoskeletal and Connective Tissue Disorders:	Arthralgia
Renal and Urinary Disorders:	Urinary incontinence, pollakiuria
Reproductive System and Breast Disorders:	Erectile dysfunction
General Disorders and Administration Site Conditions:	Peripheral edema
Investigations:	Blood creatine phosphokinase increased

There is limited information on the use of itraconazole during pregnancy. Cases of congenital abnormalities including skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations have been reported during post-marketing experience. A causal relationship with itraconazole has not been established. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

OVERDOSAGE

Itraconazole is not removed by dialysis. In the event of accidental overdosage,

supportive measures should be employed. Contact a certified poison control center for the most up to date information on the management of itraconazole oral solution overdosage (1-800-222-1222 or www.poison.org). In general, adverse events reported with overdose have been consistent with adverse drug reactions already listed in this package insert for itraconazole. (See ADVERSE REACTIONS.)

DOSAGE AND ADMINISTRATION

Treatment of Oropharyngeal and Esophageal Candidiasis:
The solution should be vigorously swished in the mouth (10 mL at a time) for several seconds and swallowed.
The recommended dosage of itraconazole oral solution for oropharyngeal candidiasis is 200 mg (20 mL) daily for 1 to 2 weeks. Clinical signs and symptoms of oropharyngeal candidiasis generally resolve within several days.

For patients with oropharyngeal candidiasis unresponsive/refractory to treatment with fluconazole tablets, the recommended dose is 100 mg (10 mL) b.i.d. For patients responding to therapy, clinical response will be seen in 2 to 4 weeks. Patients may be expected to relapse shortly after discontinuing therapy. Limited data on the safety of long-term use (>6 months) of itraconazole oral solution are available at this time.
The recommended dosage of itraconazole oral solution for esophageal candidiasis is 100 mg (10 mL) daily for a minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (20 mL) per day may be used based on medical judgment of the patient's response to therapy.
Itraconazole oral solution and itraconazole capsules should not be used interchangeably.
Patients should be instructed to take itraconazole oral solution without food, if possible.
Only itraconazole oral solution has been demonstrated effective for oral and/or esophageal candidiasis.
Use in Patients with Renal Impairment:
Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations and PRECAUTIONS.)
Use in Patients with Hepatic Impairment:
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and PRECAUTIONS.)

HOW SUPPLIED

Itraconazole Oral Solution is available in 150 mL amber glass bottles (NDC 31722-006-31) containing 10 mg of itraconazole per mL.
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze.

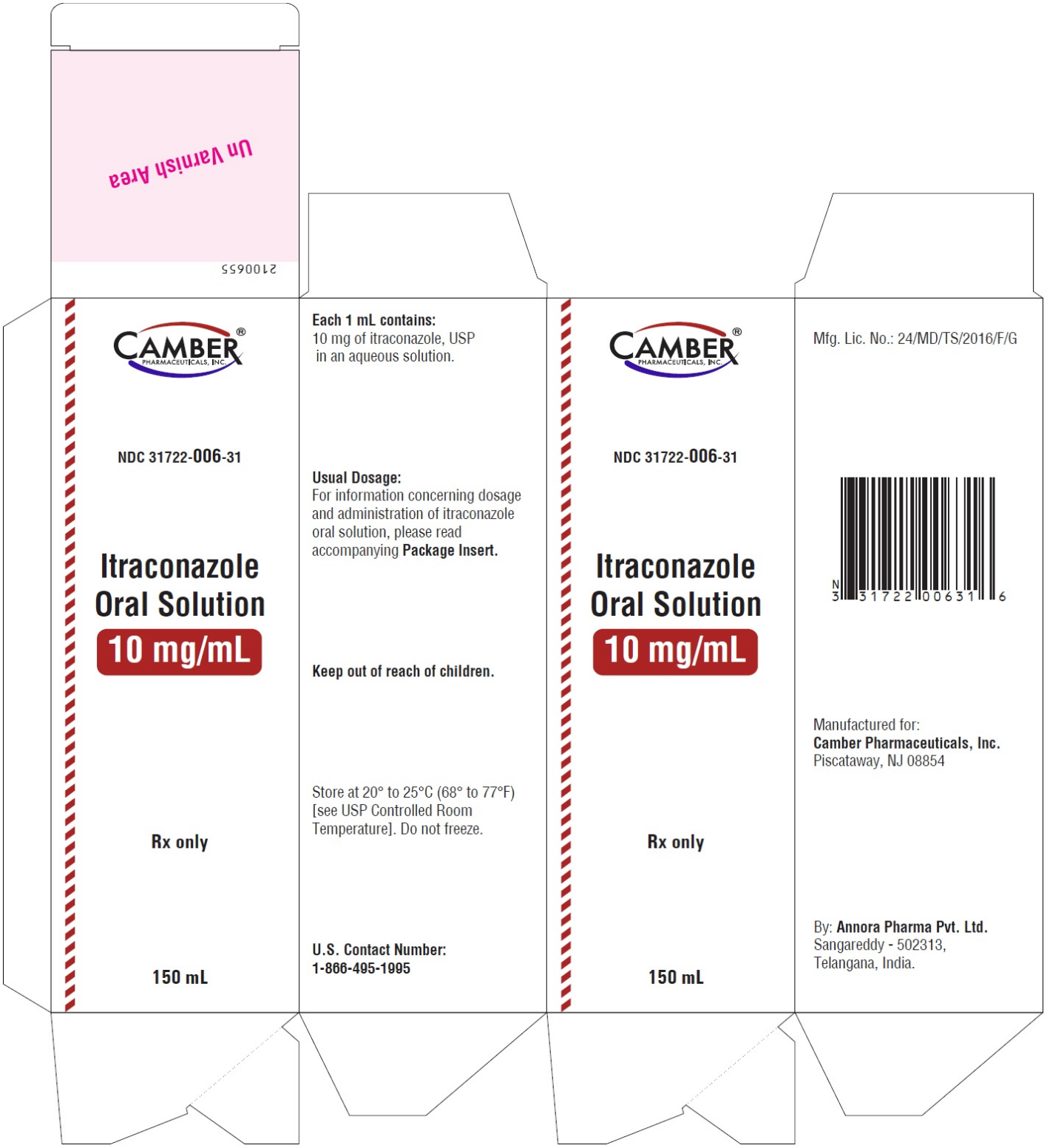
Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854.

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

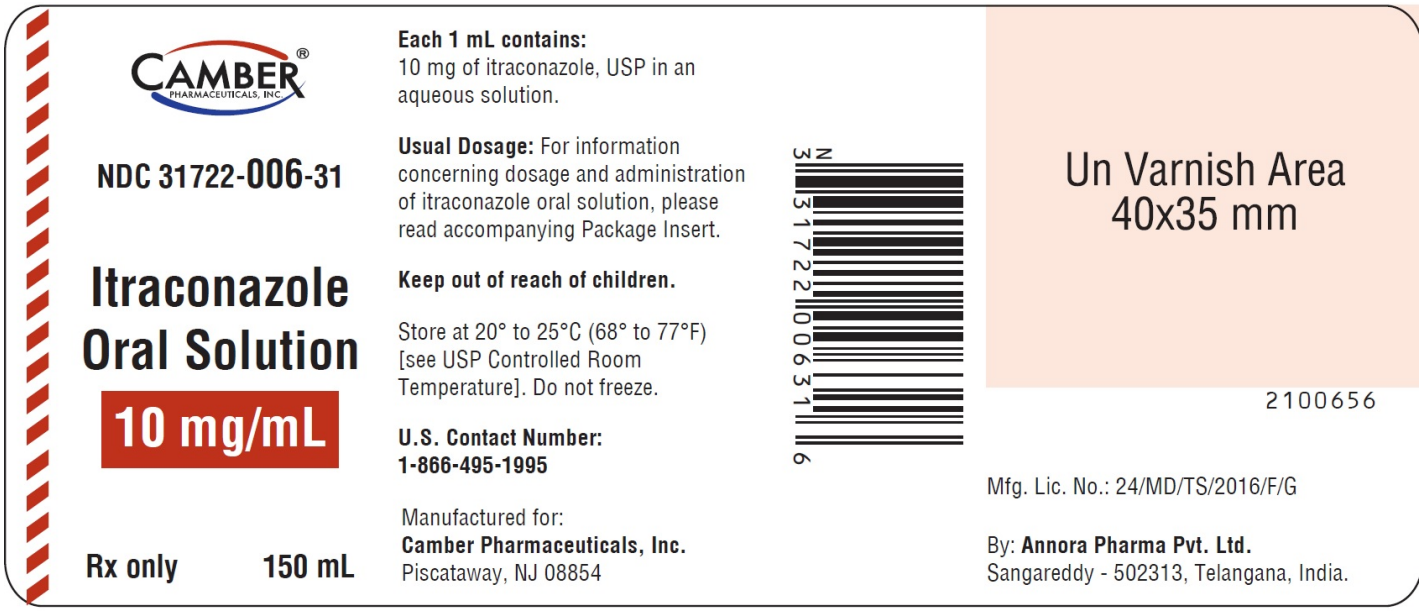
Revised: 03/2024

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Itraconazole Oral Solution 10 mg/mL carton label



Itraconazole Oral Solution 10 mg/mL container label



ITRACONAZOLE

itraconazole solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:31722-006
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ITRACONAZOLE (UNII: 304NUG5GF4) (ITRACONAZOLE - UNII:304NUG5GF4)	ITRACONAZOLE	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
ASCORBIC ACID (UNII: PQ6CK8PD0R)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
NONCRYSTALLIZING SORBITOL SOLUTION (UNII: 9E0S3UM200)	
SACCHARIN SODIUM (UNII: SB8ZUX40TY)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Product Characteristics			
Color	yellow (colorless to yellowish brown)	**Score**	
Shape		**Size**	
Flavor	CHERRY	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:31722-006-31	1 in 1 CARTON	09/01/2020	
1		150 mL in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA212239	09/01/2020	

Labeler - Camber Pharmaceuticals, Inc. (826774775)

Establishment

Name	Address	ID/FEI	Business Operations
Annora Pharma Private Limited		650980746	manufacture(31722-006)

Revised: 9/2024 Camber Pharmaceuticals, Inc.