TOLSURA- itraconazole capsule, gelatin coated
Mayne Pharma Commercial LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TOLSURA® safely and effectively. See full prescribing information for TOLSURA®.

TOLSURA® (itraconazole capsules), for oral use
Initial U.S. Approval: 1992

WARNING: CONGESTIVE HEART FAILURE and DRUG INTERACTIONS

See full prescribing information for complete boxed warning.

- **Congestive Heart Failure**
  TOLSURA can cause or exacerbate congestive heart failure (CHF). When itraconazole was administered intravenously to healthy human volunteers and dogs, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur or worsen during administration of TOLSURA, reassess the benefit-risk of continuing treatment. (5.1, 6).
- **Drug Interactions**
  - **Co-administration of certain drugs that are metabolized by human CYP3A4 enzymes are contraindicated with TOLSURA because plasma concentrations of such drugs are increased. (4.1, 5.5, 7.1)**
  - **Co-administration with colchicine, fesoterodine and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment. (4.1, 7.1)**
  - **Co-administration with eliglustat is contraindicated in poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors. (4.1, 7.1)**
  - **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. (4.1, 5.5, 7.1)**

RECENT MAJOR CHANGES

Warnings and Precautions, Pseudoaldosteronism (5.4)	10/2024

INDICATIONS AND USAGE

TOLSURA is an azole antifungal indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients (1):

- Blastomycosis, pulmonary and extrapulmonary
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Limitations of Use:
TOLSURA is not indicated for the treatment of onychomycosis (1)
TOLSURA is **NOT** interchangeable or substitutable with other itraconazole products (1)

DOSAGE AND ADMINISTRATION

- Blastomycosis and Histoplasmosis - 130 mg to 260 mg daily (2)
- Aspergillosis - 130 mg to 260 mg daily (2)
- See full prescribing information for additional dosing for life-threatening situations. (2)
- TOLSURA must be administered with food. (2)
- Swallow whole. Do not chew crush or break. (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 65 mg (3)

CONTRAINDICATIONS

- Co-administration with certain drugs that either affect metabolism of itraconazole or whose metabolism is affected by itraconazole. (4.1)
- Hypersensitivity to itraconazole (4.2)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Serious hepatotoxicity, including liver failure and death were reported with the use of itraconazole. Discontinue treatment if signs of liver dysfunction occur (5.2)
- Cardiac Dysrhythmias: Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using certain drugs that are metabolized by human CYP450 enzymes concomitantly with oral itraconazole and/or other CYP3A4 inhibitors. (4, 5.3, 5.5)
- Pseudoaldosteronism: Manifested by the onset or worsening of hypertension, and abnormal laboratory findings. Monitor blood pressure and potassium levels and manage as necessary (5.4).
- Peripheral Neuropathy: This has been reported in patients on long-term therapy with itraconazole. Monitor and promptly evaluate neurologic symptoms. (5.6)
- Hearing Loss: Reversible or permanent has been reported in patients. Discontinue treatment if hearing loss occurs (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 1%) are nausea, rash, vomiting, edema, headache, diarrhea, fatigue, fever, pruritus, hypertension, abnormal hepatic function, abdominal pain, dizziness, hypokalemia, anorexia, malaise, decreased libido, somnolence, albuminuria, impotence (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Itraconazole is mainly metabolized through CYP3A4. Other drugs that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. (4, 5, 7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CONGESTIVE HEART FAILURE and DRUG INTERACTIONS

- **Congestive Heart Failure**
  TOLSURA can cause or exacerbate congestive heart failure (CHF). When itraconazole was administered intravenously to healthy human volunteers and dogs, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur or worsen during administration of TOLSURA, reassess the benefit and risk of continuing treatment *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.
- **Drug Interactions**
  - **Co-administration of certain drugs that are metabolized by human CYP3A4 enzymes are contraindicated with TOLSURA because plasma concentrations of such drugs are increased, which may also increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs *[see Contraindications (4.1) and Drug Interactions (7.1)]***
  - **Co-administration with colchicine, fesoterodine and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment, and**
  - **Co-administration with eliglustat is contraindicated in subjects that are poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors.**
  - **Increased plasma concentrations of some of these drugs caused by co-administration with TOLSURA can lead to QT prolongation and/or ventricular tachyarrhythmias, including occurrences of *torsades de pointes*, a potentially fatal arrhythmia [see *Contraindications (4.1), Warnings and Precautions (5.5)* and *Drug Interactions (7.1)*].**

1 INDICATIONS AND USAGE

TOLSURA is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients:

- Blastomycosis, pulmonary and extrapulmonary
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained before therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-fungal therapy should be adjusted accordingly

Limitations of Use:

TOLSURA is not indicated for the treatment of onychomycosis.

TOLSURA is NOT interchangeable or substitutable with other itraconazole products due to the differences in the dosing between TOLSURA and other itraconazole products. Therefore, follow the specific dosage recommendations for TOLSURA *[see Dosage and Administration (2)].*

2 DOSAGE AND ADMINISTRATION

TOLSURA must be administered with food.

TOLSURA capsules must be swallowed whole. Do not chew, crush or break TOLSURA capsules.

Table 1 below describes the recommended dosage for TOLSURA.

Table 1: Dosage and Administration of TOLSURA

Indications	**Daily Dosing**
Treatment of Blastomycosis and Histoplasmosis	
Recommended dose	130 mg (2 × 65 mg capsules) once daily If no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 65 mg increments to a maximum of 260 mg/day (130 mg (2 × 65 mg capsules) twice daily). Doses above 130 mg/day should be given in two divided doses.
Treatment of Aspergillosis	
Recommended dose	130 mg (2 × 65 mg capsules) once daily
	260 mg/day (130 mg (2 × 65 mg capsules) twice daily)
Treatment in Life-Threatening Situations	
Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose should be used.	A loading dose of 130 mg (2 × 65 mg capsules) three times daily (390 mg/day) is recommended to be given for the first 3 days, followed by the appropriate recommended dosing based on indication. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

3 DOSAGE FORMS AND STRENGTHS

TOLSURA (itraconazole capsules) is available in a size 1, hard gelatin capsules with light

blue cap and white body, imprinted with "i-65" in black on the cap and containing 65 mg of itraconazole.

4 CONTRAINDICATIONS

4.1 Drug Interactions

- Co-administration of certain drugs that are metabolized by human CYP3A4 substrates are contraindicated with TOLSURA because plasma concentrations of such drugs are increased, which may also increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs *[see Warnings and Precaution (5.5) and Drug Interactions (7.1)]*.
- Co-administration with colchicine, fesoterodine and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment.
- Co-administration with eliglustat is contraindicated in subjects that are poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors *[see Drug Interactions (7.1)]*.
- Increased plasma concentrations of some of these drugs due to co-administration of TOLSURA can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of *torsade de pointes*, a potentially fatal arrhythmia *[*see *Drug Interactions (7.1)]*.

4.2 Hypersensitivity

TOLSURA is contraindicated in patients with known hypersensitivity to itraconazole. There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Congestive Heart Failure

TOLSURA can cause or exacerbate congestive heart failure (CHF) *[see Boxed Warning and Adverse Reactions (6.1)].* For patients with evidence of ventricular dysfunction such as CHF, history or risk factors for CHF, physicians should carefully review the risks and benefits of TOLSURA 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. Inform such patients of the signs and symptoms of CHF and monitor carefully for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear or worsen during administration of TOLSURA, reassess the benefit-risk of continuing treatment.

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was demonstrated. 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 has been associated with reports of CHF, peripheral edema, and pulmonary edema. In post-marketing experience, heart failure was more frequently reported in patients receiving higher total daily doses of itraconazole of 400 mg although there were

also cases reported among those receiving lower total daily doses *[see Adverse Reactions (6.2)]*.

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, when co-administering itraconazole and calcium channel blockers, monitor carefully for signs and symptoms of CHF during treatment due to an increased risk of CHF. Concomitant administration of TOLSURA and felodipine or nisoldipine is contraindicated *[see Contraindications (4.1), Drug Interactions (7.1) and Adverse Reactions (6.2)]*

5.2 Hepatotoxicity

Itraconazole has been associated with 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, discontinue treatment and perform testing for liver disease. Continued TOLSURA use or reinstitution of treatment with TOLSURA is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk ***[****see Adverse Reactions (6.1)].*

5.3 Cardiac Dysrhythmias

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as, pimozide, methadone, or quinidine concomitantly with oral itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with TOLSURA is contraindicated *[see Boxed Warning, Contraindications (4) and Drug Interactions (7)].*

5.4 Pseudoaldosteronism

Pseudoaldosteronism, manifested by the onset of hypertension or worsening of hypertension, and abnormal laboratory findings (hypokalemia, low serum renin and aldosterone, and elevate 11-deoxycortisol), has been reported with itraconazole use in the postmarketing setting. Monitor blood pressure and potassium levels and manage as necessary. Management of pseudoaldosteronism may include discontinuation of TOLSURA, substitution with an appropriate antifungal drug that is not associated with pseudoaldosteronism, or use of aldosterone receptor antagonists.

5.5 Drug Interaction Potential

Itraconazole has a potential for clinically important drug interactions *[see Drug Interactions (7.1, 7.2)]*. Co-administration of specific drugs with TOLSURA may result in changes in the efficacy of itraconazole and/or the co-administered drug, life-threatening effects and/or sudden death. *[see Boxed Warning, Contraindications (4.1) and Drug Interactions (7.1, 7.2)].*

5.6 Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients on long-term therapy with itraconazole. Monitor for and promptly evaluate neurologic symptoms. If neuropathy attributable to TOLSURA occurs, discontinue treatment.

5.7 Hearing Loss

Reversible or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated *[see Boxed Warning, Contraindications (4.2)* and *Drug Interactions (7)]*. The hearing loss usually resolves when treatment is stopped but can persist in some patients.

5.8 Hypersensitivity Reactions

TOLSURA is contraindicated in patients with a known hypersensitivity to itraconazole *[see Contraindications (4.2)].* Hypersensitivity reactions have been reported with the use of itraconazole *[see Adverse Reactions (6.2)]*. Due to the limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal drugs, careful enquiry about previous hypersensitivity to other azole antifungal drugs should be made when prescribing TOLSURA. If hypersensitivity reactions to TOLSURA occurs, discontinue the drug and institute appropriate therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Congestive Heart Failure *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Cardiac Dysrhythmias *[see Warnings and Precautions (5.3)]*
- Pseudoaldosteronism *[see Warnings and Precautions (5.4)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.6)]*
- Hearing Loss *[see Warnings and Precautions (5.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

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.

Adverse Reactions in the Treatment of Systemic Fungal Infections

Safety data with itraconazole capsules were derived from 602 patients treated for systemic fungal disease in U.S. clinical trials who were immunocompromised or receiving multiple concomitant medications. Treatment was discontinued in 10.5% of patients due to adverse events. The median duration before discontinuation of therapy was 81 days (range: 2 to 776 days). Table 2 lists adverse reactions reported by at least 1% of patients.

Table 2: Clinical Trials of Systemic Fungal Infections: Adverse Reactions Occurring with an Incidence of ≥1%

Body System/Adverse Reaction	Incidence (%) (N=602)
Gastrointestinal	
Nausea	11

Vomiting	5
Diarrhea	3
Abdominal Pain	2
Anorexia	1
Body as a Whole	
Edema	4
Fatigue	3
Fever	3
Malaise	1
Skin and Appendages	
Rash*	9
Pruritus	3
Central/Peripheral Nervous System	
Headache	4
Dizziness	2
Psychiatric	
Libido Decreased	1
Somnolence	1
Cardiovascular	
Hypertension	3
Metabolic/Nutritional	
Hypokalemia	2
Urinary System	
Albuminuria	1
Liver and Biliary System	
Hepatic Function Abnormal	3
Reproductive System, Male	
Impotence	1

* Rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications.

Adverse reactions reported at a rate of <1% included: constipation, gastritis, depression, insomnia, tinnitus, menstrual disorder, adrenal insufficiency, gynecomastia, and male breast pain.

Adverse Reactions Reported from Other Clinical Trials

In addition, the following adverse reactions were reported in itraconazole-treated patients who participated in clinical trials:

Hepatobiliary Disorders: hyperbilirubinemia;

Cardiac Disorders: cardiac failure, left ventricular failure, tachycardia;

General Disorders and Administration Site Conditions: face edema, chest pain, chills;

Hepatobiliary Disorders: hepatic failure, jaundice;

Investigations: alanine aminotransferase increased, aspartate aminotransferase

increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood urea increased, gammaglutamyltransferase increased, urine analysis abnormal;

Metabolism and Nutrition Disorders: hyperglycemia, hyperkalemia, hypomagnesemia;

Psychiatric Disorders: confusional state;

Renal and Urinary Disorders: renal impairment;

Respiratory, Thoracic and Mediastinal Disorders: dysphonia, cough;

Skin and Subcutaneous Tissue Disorders: hyperhidrosis;

Vascular Disorders: hypotension

6.2 Postmarketing Experience

Adverse reactions that have been identified during post-marketing experience with itraconazole are listed in Table 3. 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 3: Postmarketing 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
Endocrine Disorders:	Pseudoaldosteronism
Nervous System Disorders:	Peripheral neuropathy, paresthesia, hypoesthesia, tremor
Eye Disorders:	Visual disturbances, including blurred vision and diplopia
Ear and Labyrinth Disorders:	Transientor permanent hearing loss
Respiratory, Thoracic and Mediastinal Disorders:	Pulmonary edema, dyspnea
Gastrointestinal Disorders:	Pancreatitis, dysgeusia
Hepatobiliary Disorders:	Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis
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	Erectile dysfunction

Disorders:	Erectile dysfunction
General Disorders and Administration Site Conditions:	Peripheral edema
Investigations:	Blood creatine phosphokinase increased

7 DRUG INTERACTIONS

7.1 Effect of TOLSURA on Other Drugs

Itraconazole and its major metabolite, hydroxy-itraconazole, are potent CYP3A4 inhibitors. Itraconazole is an inhibitor of the drug transporters P-glycoprotein and breast cancer resistance protein (BCRP). Consequently, itraconazole has the potential to interact with many concomitant drugs resulting in either increased or sometimes decreased concentrations of the concomitant drugs. Increased concentrations may increase the risk of adverse reactions associated with the concomitant drug which can be severe or life-threatening in some cases (e.g., QT prolongation, *Torsade de Pointes*, respiratory depression, hepatic adverse reactions, hypersensitivity reactions, myelosuppression, hypotension, seizures, angioedema, atrial fibrillation, bradycardia, priapism). Reduced concentrations of concomitant drugs may reduce their efficacy. Table 4 lists examples of drugs that may have their concentrations affected by itraconazole, but is not a comprehensive list. Refer to the approved product labeling to become familiar with the interaction pathways, risk potential, and specific actions to be taken with regards to each concomitant drug prior to initiating therapy with itraconazole.

Although many of the clinical drug interactions in Table 4 are based on information with a similar azole antifungal, ketoconazole, these interactions are expected to occur with itraconazole.

Table 4: Drug Interactions with TOLSURA that Affect Concomitant Drug Concentrations

Concomitant Drug Within Class	**Prevention or Management**
Drug Interactions with TOLSURA that Increase Concomitant Drug Concentrations and May Increase Risk of Adverse Reactions Associated with the Concomitant Drug	
Alpha Blockers	
Alfuzosin Silodosin Tamsulosin	Not recommended during and 2 weeks after TOLSURA treatment.
Analgesics	
Methadone	Contraindicated during and 2 weeks after TOLSURA treatment.
Fentanyl	Not recommended during and 2 weeks after TOLSURA treatment.

Alfentanil Buprenorphine (IV and sublingual) Oxycodone* Sufentanil	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Antiarrhythmics	
Disopyramide Dofetilide Dronedarone Quinidine*	Contraindicated during and 2 weeks after TOLSURA treatment.
Digoxin*	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Antibacterials	
Bedaquiline†	Concomitant TOLSURA not recommended for more than 2 weeks at any time during bedaquiline treatment.
Rifabutin	Not recommended 2 weeks before, during, and 2 weeks after TOLSURA treatment. See also Table 5.
Clarithromycin	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. See also Table 5.
Trimetrexate	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Anticoagulants and Antiplatelets	
Ticagrelor	Contraindicated during and 2 weeks after TOLSURA treatment.
Apixaban Rivaroxaban Vorapaxar	Not recommended during and 2 weeks after TOLSURA treatment.
Cilostazol Dabigatran Warfarin	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Anticonvulsants	
Carbamazepine	Not recommended 2 weeks before, during, and 2 weeks after TOLSURA treatment. See also Table 5.
Antidiabetic Drugs	

Repaglinide* Saxagliptin		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Antihelminthics, Antifungals and Antiprotozoals		
Isavuconazonium		Contraindicated during and 2 weeks after TOLSURA treatment.
Praziquantel		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Artemether-lumefantrine Quinine*		Monitor for adverse reactions.
Antimigraine Drugs		
Ergot alkaloids (e.g., dihydroergotamine, ergotamine)		Contraindicated during and 2 weeks after TOLSURA treatment.
Eletriptan		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary
Antineoplastics		
Irinotecan		Contraindicated during and 2 weeks after TOLSURA treatment.
Axitinib Bosutinib Cabazitaxel Cabozantinib Ceritinib Cobimetinib* Crizotinib Dabrafenib Dasatinib	Docetaxel Ibrutinib Lapatinib Nilotinib Olaparib* Pazopanib Sunitinib Trabectedin Trastuzumab--emtansine Vinca alkaloids	Not recommended during and 2 weeks after TOLSURA treatment.
Bortezomib Brentuximab-vedotin Busulfan* Erlotinib Gefitinib* Idelalisib Imatinib Ixabepilone	Nintedanib Panobinostat Ponatinib Ruxolitinib Sonidegib Vandetanib*	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For Idelalisib, see also Table 5.
Antipsychotics, Anxiolytics and Hypnotics		
Alprazolam* Aripiprazole*	Midazolam (IV)* Quetiapine	Monitor for adverse

Aripiprazole Buspirone* Diazepam* Haloperidol*	Quetiapine Ramelteon Risperidone* Suvorexant	reactions. Concomitant drug dose reduction may be necessary.
Zopiclone*		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Lurasidone Midazolam (oral)* Pimozide Triazolam*		Contraindicated during and 2 weeks after TOLSURA treatment.
Antivirals		
Simeprevir		Not recommended during and 2 weeks after TOLSURA treatment.
Daclatasvir Indinavir* Maraviroc		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For indinavir, see also Table 5.
Cobicistat Elvitegravir (ritonavir-boosted) Ritonavir Saquinavir (unboosted)*		Monitor for adverse reactions. See also Table 5.
Tenofovir disoproxil fumarate		Monitor for adverse reactions.
Beta Blockers		
Nadolol*		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Calcium Channel Blockers		
Felodipine* Nisoldipine		Contraindicated during and 2 weeks after TOLSURA treatment.
Diltiazem Other dihydropyridines Verapamil		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For diltiazem, see also Table 5.
Cardiovascular Drugs, Miscellaneous		
Ivabradine Ranolazine		Contraindicated during and 2 weeks after TOLSURA treatment.
Aliskiren* Riociguat Sildenafil (for pulmonary hypertension)		Not recommended during and 2 weeks after TOLSURA treatment. For sildenafil and tadalafil, see also Urologic

Tadalafil (for pulmonary hypertension)		tadalafil, see also Urologic Drugs below.
Bosentan Guanfacine		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Contraceptives		
Dienogest Ulipristal		Monitor for adverse reactions.
Diuretics		
Eplerenone		Contraindicated during and 2 weeks after TOLSURA treatment.
Gastrointestinal Drugs		
Naloxegol		Contraindicated during and 2 weeks after TOLSURA treatment.
Aprepitant Loperamide*		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Netupitant		Monitor for adverse reactions.
Immunosuppressants		
Everolimus Sirolimus Temsirolimus (IV)		Not recommended during and 2 weeks after TOLSURA treatment.
Budesonide (inhalation)* Budesonide (noninhalation) Ciclesonide (inhalation) Cyclosporine (IV)* Cyclosporine (non-IV) Dexamethasone*	Fluticasone (inhalation)* Fluticasone (nasal) Methylprednisolone* Tacrolimus (IV)* Tacrolimus (oral)	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Lipid-Lowering Drugs		
Lomitapide Lovastatin* Simvastatin*		Contraindicated during and 2 weeks after TOLSURA treatment.
Atorvastatin*		Monitor for drug adverse reactions. Concomitant drug dose reduction may be necessary·
Respiratory Drugs		
		Not recommended during

Salmeterol	and 2 weeks after TOLSURA treatment.
SSRIs, Tricyclics and Related Antidepressants	
Venlafaxine	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Urologic Drugs	
Avanafil	Contraindicated during and 2 weeks after TOLSURA treatment.
Fesoterodine	*Patients with moderate to severe renal or hepatic impairment*: Contraindicated during and 2 weeks after TOLSURA treatment. *Other patients*: Monitor for adverse reactions. Concomitant drug dose reduction may be necessary
Solifenacin	*Patients with severe renal or moderate to severe hepatic impairment*: Contraindicated during and 2 weeks after TOLSURA treatment. *Other patients*: Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Darifenacin Vardenafil	Not recommended during and 2 weeks after TOLSURA treatment.
Dutasteride Oxybutynin* Sildenafil (for erectile dysfunction) Tadalafil (for erectile dysfunction and benign prostatic hyperplasia) Tolterodine	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For sildenafil and tadalafil, see also Cardiovascular Drugs above.

Miscellaneous Drugs and Other Substances	
Colchicine	*Patients with renal or hepatic impairment:* Contraindicated during and 2 weeks after TOLSURA treatment. *Other patients*: Not recommended during and 2

	weeks after TOLSURA treatment.
Eliglustat	*CYP2D6 EMs‡taking a strong or moderate CYP2D6 inhibitor, CYP2D6 IMs‡, or CYP2D6 PMs‡*: Contraindicated during and 2 weeks after TOLSURA treatment. *CYP2D6 EMs‡not taking a strong or moderate CYP2D6 inhibitor*: Monitor for adverse reactions. Eliglustat dose reduction may be necessary.
Lumacaftor/Ivacaftor	Not recommended 2 weeks before, during, and 2 weeks after TOLSURA treatment.
Alitretinoin (oral) Cabergoline Cannabinoids Cinacalcet Ivacaftor	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Vasopressin Receptor Antagonists	
Conivaptan Tolvaptan	Not recommended during and 2 weeks after TOLSURA treatment.
Drug Interactions with TOLSURA that Decrease Concomitant Drug Concentrations and May Reduce Efficacy of the Concomitant Drug	
Antineoplastics	
Regorafenib	Not recommended during and 2 weeks after TOLSURA treatment.
Gastrointestinal Drugs	
Saccharomyces boulardii	Not recommended during and 2 weeks after TOLSURA treatment.
Nonsteroidal Anti-Inflammatory Drugs	
Meloxicam*	Concomitant drug dose increase may be necessary.

* Based on clinical drug interaction information with itraconazole.
† Based on 400 mg Bedaquiline once daily for 2 weeks.
‡ EMs: extensive metabolizers; IMs: intermediate metabolizers, PMs: poor metabolizers.

7.2 Effect of Other Drugs on TOLSURA

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share

this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Some concomitant drugs have the potential to interact with TOLSURA resulting in either increased or sometimes decreased concentrations of TOLSURA. Increased concentrations may increase the risk of adverse reactions associated with TOLSURA. Decreased concentrations may reduce TOLSURA efficacy.

Table 4 lists examples of drugs that may affect itraconazole concentrations, but is not a comprehensive list. Refer to the approved product labeling to become familiar with the interaction pathways, risk potential and specific actions to be taken with regards to each concomitant drug prior to initiating therapy with TOLSURA.

Although many of the clinical drug interactions in Table 5 are based on information with a similar azole antifungal, ketoconazole, these interactions are expected to occur with TOLSURA.

Table 5: Drug Interactions with Other Drugs that Affect TOLSURA Concentrations

Concomitant Drug Within Class	**Prevention or Management**
Drug Interactions with Other Drugs that Increase TOLSURA Concentrations and May Increase Risk of Adverse Reactions Associated with TOLSURA	
Antibacterials	
Ciprofloxacin* Erythromycin* Clarithromycin*	Monitor for adverse reactions. TOLSURA dose reduction may be necessary.
Antineoplastics	
Idelalisib	Monitor for adverse reactions. TOLSURA dose reduction may be necessary. See also Table 4.
Antivirals	
Cobicistat Darunavir (ritonavir-boosted) Elvitegravir (ritonavir-boosted) Fosamprenavir (ritonavir-boosted) Indinavir* Ritonavir Saquinavir	Monitor for adverse reactions. TOLSURA dose reduction may be necessary. For, cobicistat, elvitegravir, indinavir, ritonavir, and saquinavir, see also Table 4.
Calcium Channel Blockers	
Diltiazem	Monitor for adverse reactions. TOLSURA dose reduction may be necessary. See also Table 4.
Gastrointestinal Drugs	
Drugs that reduce gastric acidity e.g. acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such	Co-administration of these drugs, including omeprazole, with TOLSURA increases the systemic exposure to itraconazole. Monitor for

as H_2- receptor antagonists and proton pump inhibitors (e.g., omeprazole).	adverse reactions. TOLSURA dose reduction may be necessary *[see Clinical Pharmacology (12.3)].*
Drug Interactions with Other Drugs that Decrease TOLSURA Concentrations and May Reduce Efficacy of TOLSURA	
Antibacterials	
Isoniazid Rifampicin*	Not recommended 2 weeks before and during TOLSURA treatment.
Rifabutin*	Not recommended 2 weeks before, during, and 2 weeks after TOLSURA treatment. See also Table 4.
Anticonvulsants	
Phenobarbital Phenytoin*	Not recommended 2 weeks before and during TOLSURA treatment.
Carbamazepine	Not recommended 2 weeks before, during, and 2 weeks after TOLSURA treatment. See also Table 4.
Antivirals	
Efavirenz* Nevirapine*	Not recommended 2 weeks before and during TOLSURA treatment.
Miscellaneous Drugs and Other Substances	
Lumacaftor/Ivacaftor	Not recommended 2 weeks before, during, and 2 weeks after TOLSURA treatment.

* Based on clinical drug interaction information with itraconazole.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on exposure to itraconazole during pregnancy for the approved indications. Published epidemiologic studies of women exposed to short courses of treatment with itraconazole in the first trimester of pregnancy have reported no risk of major birth defects overall and inconclusive findings on the risk of miscarriage *(see Data)*.

In animal reproduction studies, itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately (6-25 times the maximum recommended human dose [MRHD] of 390 mg/day based on mg/kg comparisons), and in mice at dosage levels of approximately 80

mg/kg/day (12 times the MRHD).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Published prospective and retrospective cohort studies of women exposed to short courses of treatment with itraconazole in the first trimester of pregnancy (sample size 198-687) have reported no increase in the rate of major birth defects. The most important methodological limitation of these studies is the short duration of exposure in pregnancy (mean duration 6.9 to 8.5 days), or the lack of information on treatment duration. The risk of prolonged exposure in pregnancy is not known.

Published prospective and retrospective cohort studies of pregnant women exposed to itraconazole (sample size 131-198) have reported inconsistent findings on the risk of miscarriage. Available data are inconclusive and limited by possible bias due to earlier enrollment and possible residual confounding in the exposed group compared to the unexposed group.

Animal Data

Itraconazole has been shown to cross the placenta in a rat model. In animal reproduction studies, itraconazole administration to rats and mice during organogenesis resulted in maternal toxicity, embryotoxicity and teratogenicity at and above 40 and 80 mg/kg respectively (doses equivalent to 6- and 12-times the MRHD of 390 mg/day, based on mg/kg comparisons). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

8.2 Lactation

Risk Summary

Itraconazole is excreted in human milk; however, there are no data on the amount of itraconazole in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TOLSURA and any potential adverse effects on the breastfed child from TOLSURA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

The long-term effects of itraconazole on bone growth in children are unknown. Bone lesions were observed in the young adult rats dosed with oral itraconazole for 3 to 12 months *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Clinical studies of itraconazole did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. It

is advised to use TOLSURA Capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Reversible or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated *[see Boxed Warning, Contraindications (4.1)* and *Drug Interactions (7.1)]*.

8.6 Renal Impairment

Limited data are available on the use of oral itraconazole in patients with renal impairment. It is recommended that patients with renal impairment be carefully monitored when taking TOLSURA *[see Clinical Pharmacology (12) and Warnings and Precautions (5.1)]*.

8.7 Hepatic Impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. It is recommended that patients with impaired hepatic function be carefully monitored when taking TOLSURA. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4 *[see Clinical Pharmacology (12.3)]*.

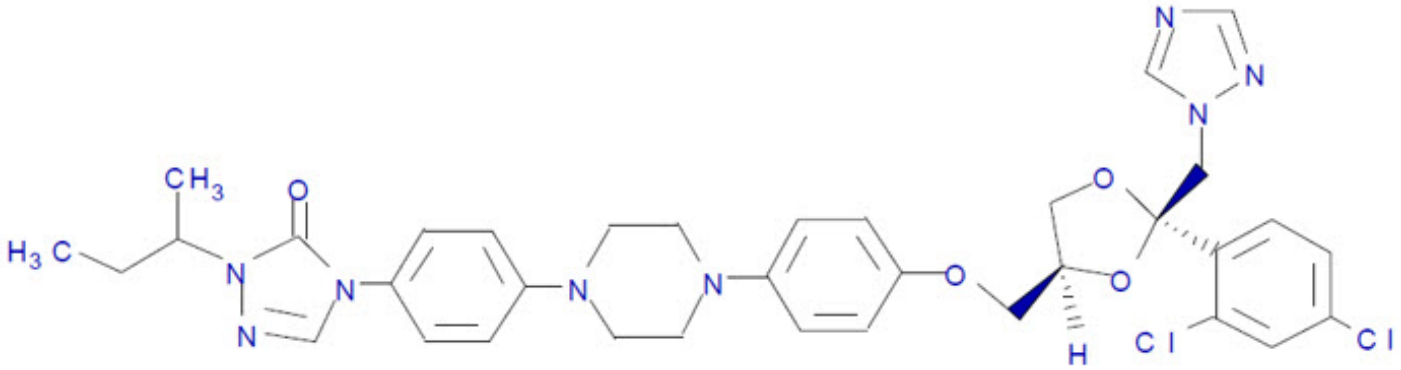
In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with TOLSURA is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications *[see Clinical Pharmacology (12) and Warnings and Precautions (5.2)].*

10 OVERDOSAGE

Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures should be employed. Activated charcoal may be given if considered appropriate.

11 DESCRIPTION

TOLSURA (itraconazole capsules) is an azole antifungal drug for oral use. Itraconazole is an equal mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:



(±)-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 $C_{35}H_{38}Cl_2N_8O_4$ 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.

Each TOLSURA capsule contains 65 mg of itraconazole dispersed in a polymer matrix and encapsulated in a hard gelatin capsule. The inactive ingredients are colloidal silicon dioxide, hypromellose phthalate, magnesium stearate and sodium starch glycolate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Itraconazole is an azole antifungal drug *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

The steady-state pharmacokinetics of itraconazole following administration of a 130 mg twice daily dose regimen of TOLSURA (2 × 65 mg) was compared with a 200 mg twice daily dose regimen of itraconazole capsules (2 × 100 mg) immediately after a meal for 14.5 days in 16 healthy volunteers; the results from this study are presented in Table 6 below

Table 6: Pharmacokinetics of Itraconazole Following Administration of TOLSURA and Itraconazole Capsules Given Twice Daily for 14.5 Days Under Fed Conditions* in

16 Healthy Subjects

Parameter†,‡	TOLSURA 130 mg twice daily (2 × 65 mg Capsules)	Itraconazole 200 mg twice daily (2 × 100 mg Capsules)
$AUC_{0\text{-}tau}$ (hr*mcg/ml)	15.6 ± 3.7	14.9 ±3.8
C_{trough} (mcg/ml)	1.2 ±0.4	1.0±0.3
$C_{max,ss}$ (mcg/ml)	1.6 ±0.4	1.5 ±0.4
$T_{max,ss}$ (h)	7.0 (1-10)	5.0 (1-8)

* Standardized high-fat, high-calorie breakfast was given 30 minutes prior to dosing on the morning of Day 15; standardized meals given prior to all other doses.
† Geometric means ± standard deviation
‡ T_{max} presented as median (range)

Peak plasma concentrations of itraconazole after administration of a single dose of TOLSURA are reached within 2 to 6 hours following oral administration in either the fasted or fed states. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing of TOLSURA. Steady-state concentrations are generally reached within about 15 days, with mean C_{max} values of 0.6 mcg/ml and 1.7 mcg/ml after oral administration of 130 mg once daily and 130 mg twice daily, respectively

Absorption

Effect of Food

The effect of food on the steady-state pharmacokinetics of itraconazole following administration of a 130 mg twice daily dose regimen of TOLSURA (2 × 65 mg) for 14.5 days under fed and fasted conditions was evaluated in 20 healthy volunteers. A high-fat meal with total caloric content of 919 calories (526 fat calories, 260 carbohydrate calories and 133 protein calories) was used in the study. The results are shown in Table 7 below.

Table 7: Pharmacokinetic Parameters of Itraconazole Following Administration of TOLSURA 130 mg (2 × 65 mg capsules) Given Twice Daily for 14.5 Days Under Fed and Fasted Conditions in 20 Healthy Subjects

Parameter	Treatment	Geometric Mean	Fed/Fasted Ratio (%)	90% Confidence Interval
C_{max_ss} (mcg/mL)	**Fed**	1.4 ± 0.6	73.7	69.0, 77.3
	Fasted	1.9 ± 0.9		
$C_{trough,ss}$ (mcg/mL)	**Fed**	1.0 ± 0.3	90.0	86.4, 97.0
	Fasted	1.1 ± 0.6		

AUC_{tau} (hr*mcg/mL)	**Fed**	13.4 ± 5.0	78.4	74.5, 81.9
	Fasted	17.1 ± 8.0		
		Median	**Range**	
T_{max} (hr)	**Fed**	4.00	0.5 to 10	
	Fasted	3.50	0.5 to 5	

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.

Elimination

The terminal half-life of itraconazole following repeated dose administration of TOLSURA ranges between 34 to 42 hours under fed conditions.

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 hydroxyitraconazole 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.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4-week treatment and in nail keratin - where itraconazole can be detected as early as 1 week after start of treatment - for at least six months after the end of a 3-month treatment period.

Specific Populations

Patients with 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_{0-8h}). Plasma concentration versus-time profiles showed wide intersubject variation in all three groups. After a single intravenous 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 50-79 ml/min), moderate (defined in this study as CrCl 20-49 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 42-49 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.

Patients with 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 capsules. A statistically significant reduction in mean C_{max} (47%) and a twofold 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.

Drug Interaction Studies

Omeprazole

The effect of multiple daily oral 40 mg doses (steady-state conditions) of the proton pump inhibitor, omeprazole, on the exposure to itraconazole from a single 130 mg dose of TOLSURA (2 × 65 mg capsules) when dosed under fasted conditions was evaluated in 30 healthy adult subjects. As illustrated in Table 8 below, the mean itraconazole AUC_∞ was 22% higher and mean C_{max} 31% higher when TOLSURA was co-administered with omeprazole.

Table 8: Pharmacokinetics of Itraconazole Following Single Dose Administration of TOLSURA 130 mg (2 × 65mg capsules) Alone or with Omeprazole 40 mg QD Administered for 7 Days Under Fasted Conditions in Healthy Volunteers

Parameter	Treatment A* Mean ±SD	Treatment A + B† Mean ±SD	Treatment A+B vs Treatment A Ratio %	90% Confidence Interval
AUC_∞	2846.3	3477.9 ±	122.2	108.7, 137.3

(h•ng/mL)	±1644.4	1572.6	122.2	108.7, 137.3
C_{max} (ng/mL)	212.9 ± 119.1	278.8 ±106.8	130.9	111.4, 153.8
T_{max}‡ (h)	3.5 (2.0 -5.0)	3.3 (1.5 – 5.0)	-	-

* Treatment A: TOLSURA
† Treatment B: Omeprazole
‡ T_{max} is given as median (Range)

12.4 Microbiology

Mechanism of Action

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent, ^{14}C-demethylation of ergosterol, which is a vital component of fungal cell membranes.

Resistance

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy. Several *in vitro* studies have reported that some fungal clinical isolates 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 performed.

Itraconazole is not active against *Zygomycetes* (e.g., *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

Interaction with Other Antimicrobials

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. 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 this finding is unknown.

Antifungal Activity

Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus,* and *Trichophyton* species *[see Indications and Usage (1)]*. Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for

23 months at dosage levels up to 80 mg/kg/day (approximately 12×MRHD, based on mg/kg comparisons). Male rats treated with 25 mg/kg/day (4×MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (8×MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Mutagenesis

Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Impairment of Fertility

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (6×MRHD, based on mg/kg comparisons), even though parental toxicity was present at this dosage level.

13.2 Animal Toxicology and/or Pharmacology

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented.

In three toxicology studies using rats, itraconazole (dosed in feed or via oral gavage) induced bone defects at dosage levels as low as 20 mg/kg/day (3×MRHD, based on mg/kg comparisons). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (12×MRHD) over 1 year or 160 mg/kg/day (25×MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats.

14 CLINICAL STUDIES

Overview of the Clinical Studies

Clinical studies in invasive mycoses listed in this section were conducted with itraconazole 100 mg capsules. Dosage for TOLSURA is different from that of other itraconazole formulations. TOLSURA is not interchangeable or substitutable with other itraconazole products *[see Indications and Usage (1), Dosage and Administration (2) and Clinical Pharmacology (12.3)]*

14.1 Blastomycosis

Analyses were conducted on data from two open-label, non-concurrently controlled studies (N=73 combined) in patients with normal or abnormal immune status treated with the100 mg itraconazole capsules. The median dose was 200 mg/day (2 × 100 mg).

A response for most signs and symptoms was observed within the first 2 weeks, and all signs and symptoms cleared between 3 and 6 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole for the treatment of blastomycosis compared with the natural history of untreated cases.

14.2 Histoplasmosis

Analyses were conducted on data from two open-label, non-concurrently controlled studies (N=34 combined) in patients with normal or abnormal immune status (not including HIV-infected patients) treated with the 100 mg itraconazole capsules. The median dose was 200 mg/day (2 × 100 mg). A response for most signs and symptoms was observed within the first 2 weeks, and all signs and symptoms cleared between 3 and 12 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole for the treatment of histoplasmosis, compared with the natural history of untreated cases.

14.3 Histoplasmosis in HIV-infected Patients

Data from a small number of HIV-infected patients treated with the 100 mg itraconazole capsules suggested that the response rate of histoplasmosis in HIV-infected patients is similar to that of non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse.

14.4 Aspergillosis

Analyses were conducted on data from an open-label, "single-patient-use" protocol designed to make itraconazole available in the U.S. for patients who either failed or were intolerant of amphotericin B therapy (N=190). The findings were corroborated by two smaller open-label studies (N=31 combined) in the same patient population. Most adult patients were treated with a daily dose of 200 (2 × 100 mg) to 400 (4 × 100 mg) mg, with a median duration of 3 months. Results of these studies demonstrated substantial evidence of effectiveness of the 100 mg itraconazole capsules as a second-line therapy for the treatment of aspergillosis compared with the natural history of the disease in patients who either failed or were intolerant of amphotericin B therapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

TOLSURA (itraconazole capsules) is supplied in a size 1, hard gelatin capsules with light blue cap and white body, imprinted with "i-65" in black on the cap and containing 65 mg of itraconazole.

TOLSURA capsules are supplied as follows:

Bottles of 8 capsules	Bottles of 60 capsules
NDC 51862-462-88	NDC 51862-462-60

Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Important Administration Instructions

Instruct the patients that TOLSURA:

- Cannot be interchanged or substituted with other itraconazole products.
- Must be swallowed whole and administered with food.

Congestive Heart Failure

Inform patients about the signs and symptoms of congestive heart failure. Instruct them to discontinue TOLSURA and contact their healthcare provider immediately, if these signs or symptoms occur during TOLSURA administration *[see Warnings and Precautions (5.1)]*.

Hepatoxicity

Instruct patients to stop TOLSURA treatment immediately and contact their healthcare provider if any signs and symptoms suggestive of liver dysfunction develop. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine, or pale stools *[see Warnings and Precautions (5.2)]*.

Use with Proton Pump Inhibitors and Potential Drug Interactions

Advise patients to discuss with their physician the use of TOLSURA with proton pump inhibitors, such as omeprazole. Instruct patients to contact their physician before taking any other concomitant medications with TOLSURA to ensure there are no potential drug interactions *[see Contraindications (4.1, 4.2), Warnings and Precautions (5.5) and Drug interactions (7.2)]*.

Hearing Loss

Instruct patients that hearing loss can occur with the use of TOLSURA. The hearing loss usually resolves when treatment is stopped but can persist in some patients. Advise patients to inform their healthcare provider if any hearing loss symptoms occur *[see Warnings and Precautions (5.7)]*.

Vision Problem

Instruct patients that dizziness or blurred/double vision can sometimes occur with TOLSURA. Advise patients that if they experience these dizziness or blurred/double vision, they should contact their healthcare provider, and instruct the patient not to drive or use machines *[see Adverse Reactions (6.1)]*.

Pregnancy

Advise patients to notify their physician if they become pregnant or intend to become pregnant during therapy *[see Use in Specific Populations (8.1)]*.

Mayne Pharma

Raleigh, NC 27609

TOLSURA is a registered trademark of Mayne Pharma.

Patient Information

TOLSURA (tol sur ah)
(itraconazole capsules)

Read this Patient Information that comes with TOLSURA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about TOLSURA?
TOLSURA can cause serious side effects, including:

1. **Congestive heart failure.** TOLSURA can cause congestive heart failure or make congestive heart failure that you already have worse. **Stop taking TOLSURA and call your doctor right away if you have any of these symptoms of congestive heart failure:**

- shortness of breath
- swelling of your feet, ankles or legs
- sudden weight gain
- increased tiredness
- coughing up white or pink mucus (phlegm)
- fast heartbeat
- waking up at night more than normal for you

2. **Heart problems and other serious medical problems.** Serious medical problems that affect the heart and other parts of your body can happen if you take TOLSURA with certain other medicines.

- **Do not take TOLSURA if you take any of the following medicines:**
  - avanafil
  - disopyramide
  - dofetilide
  - dronedarone
  - eplerenone
  - ergot alkaloids (such as dihydroergotamine or ergotamine)
  - felodipine
  - irinotecan
  - isavuconazonium
  - ivabradine
  - lomitapide
  - lovastatin
  - lurasidone
  - methadone
  - midazolam (taken by mouth)
  - naloxegol
  - nisoldipine
  - pimozide
  - quinidine
  - ranolazine
  - simvastatin
  - ticagrelor
  - triazolam
- **Do not take TOLSURA if you have kidney or liver problems and take any of the following medicines:**
  - colchicine
  - fesoterodine
  - solifenacin
- **Do not take TOLSURA:**
  - if you have been told that an enzyme in your body, called CYP2D6, breaks down (metabolizes) certain medicines in your body too slowly.
  - if you are taking the medicine eliglustat **and** are also taking a medicine that

slows the rate that your body breaks down (metabolizes) certain other medicines (CYP2D inhibitor). Ask your doctor or pharmacist if you take any of these medicines.

These are not complete lists of medicines that can interact with TOLSURA. TOLSURA may affect the way other medicines work, and other medicines may affect how TOLSURA works. You can ask your pharmacist for a list of medicines that interact with TOLSURA.

Before you start taking TOLSURA, tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Before you start any new medicine, ask your doctor or pharmacist if it is safe to take it with TOLSURA **or within 2 weeks after stopping treatment with TOLSURA.**

3. **Liver problems.** TOLSURA can cause serious liver problems which may be severe and lead to death. **Stop taking TOLSURA and call your doctor right away if you have any of these symptoms of liver problems:**

- unusual fatigue
- loss of appetite
- nausea or vomiting
- your skin or the white part of your eyes turn yellow (jaundice)
- dark (tea-colored) urine
- light-colored stools (bowel movement)

For more information about side effects, see "**What are the possible side effects of TOLSURA?**"

What is TOLSURA?

TOLSURA is a prescription medicine used to treat the following fungal infections in adults: blastomycosis, histoplasmosis, and aspergillosis.

TOLSURA is not for use for the treatment of fungal infections of the toenails or fingernails (onychomycosis).

TOLSURA is not for use in place of other medicines that contain itraconazole.

It is not known if TOLSURA is safe and effective in children.

Do not take TOLSURA if you:

- See "**What is the most important information I should know about TOLSURA?**"
- are allergic to itraconazole or any of the ingredients in TOLSURA. See the end of this Patient Information leaflet for a complete list of ingredients in TOLSURA.

Before taking TOLSURA, tell your doctor about all of your medical conditions, including if you:

- have heart problems.
- have lung problems.
- have kidney problems.
- have liver problems.
- have had an allergic reaction to a medicine used to treat a fungal infection.
- are pregnant or plan to become pregnant. It is not known if TOLSURA will harm your unborn baby. Tell your doctor if you become pregnant during treatment with TOLSURA.
- are breastfeeding or plan to breastfeed. TOLSURA can pass into your breast milk.

Talk to your doctor about the best way to feed your baby if you take TOLSURA.

Before you start taking TOLSURA, tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your doctor if you take:

- a medicine to treat high blood pressure or certain other heart problems called a calcium channel blocker.
- a medicine to reduce acid in your stomach called a proton pump inhibitor, such as omeprazole.

How should I take TOLSURA?

- Take TOLSURA exactly as prescribed by your doctor. Your doctor will tell you how much TOLSURA to take and when to take it.
- TOLSURA **must** be taken with food.
- TOLSURA capsules **must** be swallowed whole.
- **Do not** chew, crush or break TOLSURA capsules.
- If you take too much TOLSURA, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking TOLSURA?

- TOLSURA can cause dizziness and vision problems. **Do not** drive or operate machinery until you know how TOLSURA affects you. Tell your doctor if you get dizziness or vision problems.

What are the possible side effects of TOLSURA?
TOLSURA may cause serious side effects, including:

- See "**What is the most important information I should know about TOLSURA?**"
- **New or worsening high blood pressure and low potassium levels in your blood (pseudoaldosteronism).** Your healthcare provider should check your blood pressure and potassium levels.
- **Nerve problems (neuropathy).** Nerve problems have happened in some people who have taken TOLSURA for longer than 3 months. Call your doctor right away if you have tingling or numbness in your hands or feet. Your doctor may stop your treatment with TOLSURA if you have nerve problems.
- **Hearing loss.** Hearing loss can happen in some people who take TOLSURA. Hearing loss usually improves when treatment with TOLSURA is stopped, but hearing loss has been permanent in some people. Call your doctor if you have any changes in your hearing.

The most common side effects of TOLSURA include:

- nausea
- rash
- vomiting
- swelling
- headache
- diarrhea
- fever
- itching
- high blood pressure
- abnormal liver blood tests
- stomach pain
- dizziness
- loss of appetite
- general feeling of discomfort
- decreased sex drive
- sleepiness
- elevated levels of a type of protein, called

- fatigue
- low blood potassium levels
- albumin, in your urine
- erectile dysfunction

These are not all the possible side effects of TOLSURA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TOLSURA?

- Store TOLSURA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep TOLSURA in a tightly closed container.
- Keep TOLSURA away from light.

Keep TOLSURA and all medicines out of the reach of children.

General information about the safe and effective use of TOLSURA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TOLSURA for a condition for which it was not prescribed. Do not give TOLSURA to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your doctor or pharmacist for information about TOLSURA that is written for health professionals.

What are the ingredients in TOLSURA?

Active ingredient: itraconazole
Inactive ingredients: colloidal silicon dioxide, hypromellose phthalate, magnesium stearate and sodium starch glycolate
Manufactured by: Mayne Pharma
For more information, go to www.maynepharma.com or call 1-844-825-8500

This Patient Information has been approved by the U.S. Food and Drug Administration.
Issued: 10/2024

PRINCIPAL DISPLAY PANEL - 65 mg Capsule Bottle Label

NDC 51862-462-60

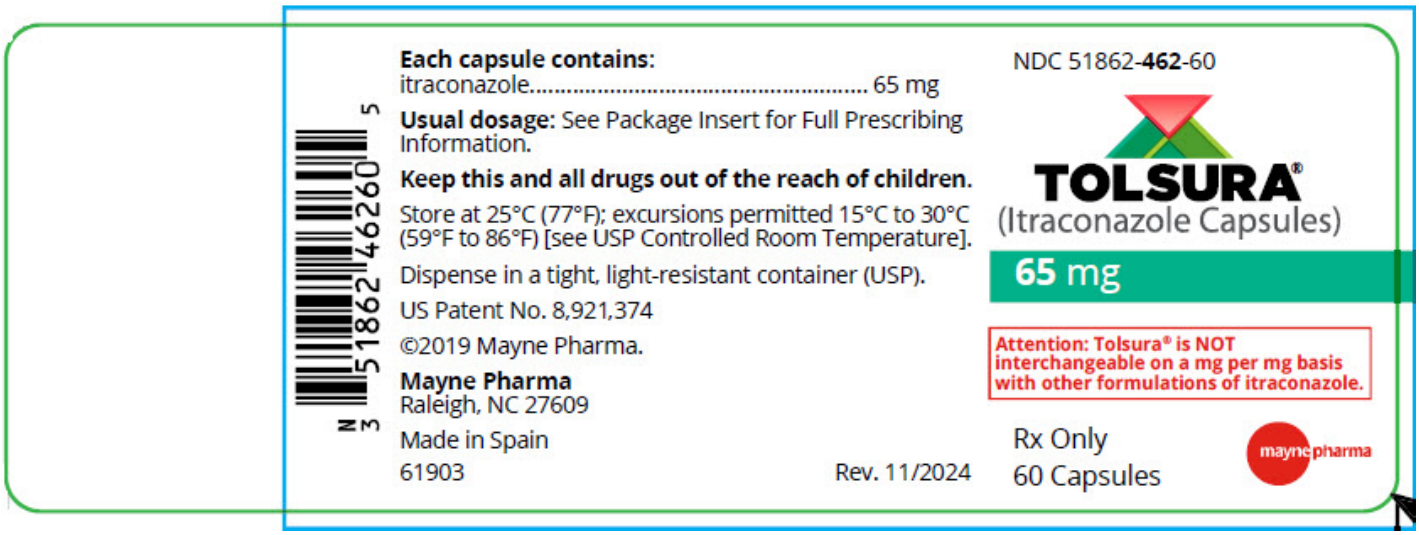
TOLSURA®
(Itraconazole Capsules)

65 mg

Attention: Tolsura® is NOT
interchangeable on a mg per mg basis
with other formulations of itraconazole.

Rx Only
60 Capsules

mayne pharma



TOLSURA

itraconazole capsule, gelatin coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-462
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ITRACONAZOLE (UNII: 304NUG5GF4) (ITRACONAZOLE - UNII:304NUG5GF4)	ITRACONAZOLE	65 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSE PHTHALATE (24% PHTHALATE, 55 CST) (UNII: 87Y6436BKR)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHYLENE CHLORIDE (UNII: 588X2YUY0A)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	

Product Characteristics			
Color	blue (Light blue) , white	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	i;65
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-462-60	60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/11/2018	
2	NDC:51862-462-88	8 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/01/2020	02/29/2024
3	NDC:51862-462-08	8 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	12/11/2018	02/29/2024

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA208901	12/11/2018	

Labeler - Mayne Pharma Commercial LLC (867220261)

Establishment

Name	Address	ID/FEI	Business Operations
Mayne Pharma International Pty Ltd		756003745	manufacture(51862-462) , analysis(51862-462)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Greenville, Inc.		118812386	label(51862-462) , pack(51862-462) , analysis(51862-462)

Revised: 4/2025 Mayne Pharma Commercial LLC