Clinical Policy Title:	itraconazole
Policy Number:	RxA.284
Drug(s) Applied:	Sporanox®, Tolsura®
Original Policy Date:	02/07/2020
Last Review Date:	07/18/2022
Line of Business Policy Applies to:	All lines of business

Background

Itraconazole (Sporanox®, Tolsura®) is an azole antifungal agent.

Sporanox® and Tolsura® capsules are indicated in:

- Immunocompromised and non-immunocompromised patients for the treatment of:
  - Blastomycosis, pulmonary and extrapulmonary
  - Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis
  - Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy

Sporanox® capsules are also indicated for the treatment of the following fungal infections in:

- Non-immunocompromised patients for the treatment of:
  - Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium)
  - Onychomycosis of the fingernail due to dermatophytes (tinea unguium)

Sporanox® oral solution is indicated for the treatment of oropharyngeal and esophageal candidiasis.

Limitations of Use:

- Tolsura® is not indicated for the treatment of onychomycosis
- Tolsura® is not interchangeable or substitutable with other itraconazole products

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
itraconazole (Sporanox®) capsule	Blastomycosis	200 mg orally once daily	400 mg/day
	Histoplasmosis	200 mg orally once daily	400 mg/day
	Aspergillosis	200 to 400 mg orally once daily	400 mg/day
	Onychomycosis	200 mg orally once daily (toenails with or without fingernail involvement) 200 mg orally Twice daily for 1 week, followed by no drug	400 mg/day

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		for 3 weeks, then another week of 200 mg orally Twice daily (fingernail only)	
itraconazole (Sporanox®) capsule	In life-threatening situations	Loading dose of 200 mg orally Three times daily given for the first 3 days of treatment	600 mg/day
itraconazole (Sporanox®) oral solution	Oropharyngeal candidiasis	200 mg (20 mL) orally daily for 1 to 2 weeks; swish in the mouth (10 mL at a time) for several seconds and swallow	200 mg (20 mL)/day
	Esophageal candidiasis	100 mg (10 mL) orally daily for a minimum treatment of three weeks	200 mg (20 mL)/day
itraconazole (Tolsura®)	Blastomycosis, Histoplasmosis	130 mg orally once daily. Increase dose if no obvious improvement or evidence of progressive fungal disease in 65 mg increments. Doses above 130 mg/day should be given in divided doses.	260 mg/day
	Aspergillosis	130 mg orally once daily or 260 mg/day Twice daily	260 mg/day
	In life-threatening situations	130 mg three times daily (390 mg/day) is recommended to be given for the first 3 days	390 mg/day

Dosage Forms

- Itraconazole (Sporanox®): Capsules 100 mg, Oral solution 10 mg/mL.
- Itraconazole (Tolsura®): Capsules 65 mg.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the

terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Onychomycosis (must meet all)**:**

1. Request is for Sporanox® capsules;
2. Member meets one of the following (a or b):
   a. For fingernail disease: Failure of a 6-week trial of oral terbinafine at 250 mg/day, unless contraindicated or clinically significant adverse effects are experienced;
   b. For toenail disease: Failure of a 12-week trial of oral terbinafine at 250 mg/day, unless contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 400 mg per day;
   a. Approval Duration

Commercial: Fingernail disease: 2 months; toenail disease: 3 months
Medicaid: Fingernail disease: 2 months; toenail disease: 3 months

B. Oropharyngeal Candidiasis (must meet all):

1. Diagnosis of oropharyngeal candidiasis;
2. Request is for Sporanox® oral solution;
3. Failure of 14-days trial at least one of the following oropharyngeal Candidiasis therapies unless contraindicated of clinically significant adverse effects are experienced (a or b):
   a. nystatin suspension
   b. clotrimazole troches/lozenges
4. Failure of a 14-day trial of fluconazole, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 200 mg (20 mL) per day.

Approval Duration
Commercial: 28 days
Medicaid: 28 days

C. Esophageal Candidiasis (must meet all):

1. Diagnosis of esophageal candidiasis;
2. Request is for Sporanox® oral solution;
3. Failure of a 21-day trial of fluconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 200 mg (20 mL) per day.

Approval Duration
Commercial: 28 days
Medicaid: 28 days

D. Aspergillosis (must meet all):

1. Diagnosis of aspergillosis;
2. Request is for Sporanox® or Tolsura® capsules;
3. Failure of a 3-month trial of voriconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
4. For Tolsura® requests, failure of generic itraconazole capsules unless contraindicated or clinically significant adverse effects are experienced (e.g., contraindications to the excipients);
5. Dose does not exceed one of the following (a or b):

a. Sporanox®: 400 mg per day;
b. Tolsura®: 260 mg per day.

Approval Duration
Commercial: 3 months
Medicaid: 3 months

E. Blastomycosis or Histoplasmosis (must meet all)**:**
1. Diagnosis of blastomycosis or histoplasmosis;
2. Request is for Sporanox® or Tolsura® capsules;
3. For Tolsura® requests, failure of generic itraconazole capsules unless contraindicated or clinically significant adverse effects are experienced (e.g., contraindications to the excipients);
4. Dose does not exceed one of the following (a or b):
   a. Sporanox®: 400 mg per day;
   b. Tolsura®: 260 mg per day.

Approval Duration
Commercial: Blastomycosis: 6 months; Histoplasmosis: 42 days
Medicaid: Blastomycosis: 6 months; Histoplasmosis: 42 days

F. Hematologic Malignancy (off-label) (must meet all)**:**
1. Diagnosis of hematologic malignancy;
2. Request is for Sporanox®;
3. Member meets one of the following (a or b):
   a. Request is for prophylaxis of aspergillosis;
   b. Request is for prophylaxis of candidiasis, and member has failed fluconazole at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 400 mg per day.
   a. **Approval Duration**

Commercial: 3 months
Medicaid: 3 months

II. Continued Therapy Approval

A. Onychomycosis (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Member has not received more than 90 days of treatment;
4. If request is for a dose increase, new dose does not exceed 400 mg per day.

Approval Duration
Commercial: Fingernail disease: 2 months; toenail disease: 3 months
Medicaid: Fingernail disease: 2 months; toenail disease: 3 months

B. Oropharyngeal/Esophageal Candidiasis (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Request is for Sporanox® oral solution;
4. If request is for a dose increase, new dose does not exceed 200 mg (20 mL) per day.

Approval Duration

Commercial: 14 days
Medicaid: 14 days

C. Blastomycosis, Histoplasmosis, or Aspergillosis (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. Request is for Sporanox® or Tolsura® capsules;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Sporanox® capsules: 400 mg per day;
   b. Tolsura®: 260 mg per day.

Approval Duration
Commercial: Blastomycosis: 6 months; Histoplasmosis: 42 days; Aspergillosis: 3 months
Medicaid: Blastomycosis: 6 months; Histoplasmosis: 42 days; Aspergillosis: 3 months

D. Hematologic Malignancy (off-label) (must meet all):

E. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
1. Request for Sporanox®;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 400 mg per day.
   a. Approval Duration

Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
CHF: Congestive heart failure

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
terbinafine	250 mg orally once daily	500 mg per day
nystatin suspension	400,000 to 600,000 units (4 to 6 mL) per dose swished in the mouth Four times daily	2.4 million units per day
clotrimazole troches/lozenges	10 mg troche orally 5 times daily for 14 days	Varies
Fluconazole (Diflucan®)	400 mg orally per day	800 mg per day
voriconazole (Vfend®)	Weight ≥ 40 kg: 200 mg orally every 12 hours Weight < 40 kg: 100 mg orally every 12 hours	Weight ≥ 40 kg: 800 mg per day Weight < 40 kg: 400 mg per day

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and

brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications*/Boxed Warnings

- Contraindication(s):
  - Itraconazole should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF.
  - Concomitant coadministration of itraconazole with the following drugs: methadone, dofetilide, quinidine, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), felodipine, pimozide, oral midazolam, triazolam, nisoldipine, cisapride, lovastatin, simvastatin.
  - Additional product-specific drug-drug interactions include:
    - Onmel™: levacetylmethadol (levomethadyl)
    - Sporanox®: (capsules and oral solution) and Tolsura®: disopyramide, dronedarone, irinotecan, lurasidone, ivabradine, ranolazine, eplerenone, ticagrelor, digoxin, isavuconazonium, naloxegol, lomitapide, avanafil, in subjects with varying degrees of renal or hepatic impairment, colchicine, fesoterodine, and solifenacin. 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 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.
    - Sporanox®: capsules: telithromycin, isavuconazole
    - Sporanox®: oral solution, levacetylmethadol (levomethadyl), isavuconazole
  - Pregnancy, or women contemplating pregnancy
  - Hypersensitivity to itraconazole

  * Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - CHF or history of CHF (see contraindications)
  - Drug-drug interactions (see contraindications)

APPENDIX D: General Information

- Inform patients about the signs and symptoms of congestive heart failure. Instruct them to discontinue itraconazole and contact their healthcare provider immediately, if these signs or symptoms occur during treatment.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of Business Policy Applies to was updated to "All lines of business". 3. Initial and Continued approval duration was updated to include Medicaid, Commercial & HIM approval duration. 4. Continued therapy criteria II.A.1, II.B.1, II.C.1 & II.D.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…".	07/22/2020	09/14/2020

5. Updated Appendix A: added CHF. 6. References were reviewed and updated.		
Policy was reviewed: 1. Approval durations for HIM were removed. 2. Appendix B (Therapeutic Alternatives): Fixed header verbiage was updated as 'Below are suggested therapeutic alternatives.' Discontinued brands Lamisil®, and Mycelex® were removed. 3. Appendix C: Contraindication(s) was updated. 4. Appendix D: General Information was added. 5. References were updated.	04/15/2021	06/10/2021
Policy was reviewed: 1. RxA.284, Drug(s) Applied: Updated to remove discontinued drug Onmel; Onmel removed from rest of the policy. 2. Background: Updated to include limitation(s) of use: 3. Tolsura® is not indicated for the treatment of onychomycosis 4. Tolsura® is not interchangeable or substitutable with other itraconazole products 5. Dosing Information, Dosing Regimen, Tolsura®: Updated dosing information from 130 mg orally once daily or Twice daily to 130 mg orally once daily or 260 mg/day Twice daily for indication Aspergillosis. 6. Dosing Information, Indication: Updated to include new indication in life-threatening situations. 7. Dosing Information, Dosing Regimen, Tolsura: Updated to include dosing information for indication In life-threatening situations. 8. Dosing Information, Maximum Dose, Tolsura: Updated to include maximum dosing information for indication In life-threatening situations. 9. Initial Approval Criteria, 1.B.3: Updated trial and failure criteria from Failure of a 14-day trial of nystatin suspension or clotrimazole troches/lozenges, unless contraindicated or clinically significant adverse effects are experienced to Failure of 14-days trial at least one of the following oropharyngeal Candidiasis therapies unless contraindicated of clinically	01/10/2022	04/18/2022

significant adverse effects are experienced (a or b): a. nystatin suspension b. clotrimazole troches/lozenges 10. Initial Approval Critiera, I.F: Updated to remove Tolsura. 11. Continued Therapy Approval Criteria II.A.1, II.B.1, II.C.1 & II.D .1 were rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 12. Continued Approval Criteria, II.D: Updated to remove Tolsura. 13. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only" 14. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 15. References were reviewed and updated.		
Policy was reviewed: 1. Initial Approval Criteria, I.D.4 and I.E.3: Updated verbiage to “, failure of generic itraconazole capsules unless contraindicated or clinically significant adverse effects are experienced” from “Documentation supports…”.	6/25/2022	7/18/2022