Clinical Policy: Itraconazole (Sporanox)

Reference Number: ERX.NPA.25
Effective Date: 06.01.15
Last Review Date: 05.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Itraconazole (Sporanox®) is an azole antifungal agent.

FDA Approved Indication(s)
Sporanox 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
- 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.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Sporanox is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of onychomycosis;
2. Request is for Sporanox or itraconazole capsules;
3. If request is for brand Sporanox, member must use generic itraconazole capsules, unless contraindicated or clinically significant adverse effects are experienced;
4. 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 per 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 per day, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 400 mg (4 capsules) per day.

Approval duration:
Fingernail disease: 2 months
Toenail disease: 3 months

B. Oropharyngeal Candidiasis (must meet all)**:**
1. Diagnosis of oropharyngeal candidiasis;
2. Request is for Sporanox or itraconazole oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of a 14-day trial of nystatin suspension or clotrimazole troches/lozenges, unless clinically significant adverse effects are experienced or both are contraindicated;
5. Failure of a 14-day trial of fluconazole, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 200 mg (20 mL) per day.

Approval duration: 4 weeks

C. Esophageal Candidiasis (must meet all)**:**
1. Diagnosis of esophageal candidiasis;
2. Request is for Sporanox or itraconazole oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of a 21-day trial of fluconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 200 mg (20 mL) per day.

Approval duration: 4 weeks

D. Aspergillosis (must meet all)**:**
1. Diagnosis of aspergillosis;
2. Request is for Sporanox or itraconazole capsules;
3. If request is for brand Sporanox, member must use generic itraconazole capsules, unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of a 3-month trial of voriconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 400 mg (4 capsules) per day.

Approval duration: 3 months

E. Blastomycosis or Histoplasmosis (must meet all)**:**
1. Diagnosis of blastomycosis or histoplasmosis;
2. Request is for Sporanox or itraconazole capsules;
3. If request is for brand Sporanox, member must use generic itraconazole capsules, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 400 mg (4 capsules) per day.

Approval duration:
Blastomycosis: 6 months
Histoplasmosis: 6 weeks

F. Hematologic Malignancy (off-label) (must meet all)**:**
1. Diagnosis of hematologic malignancy;
2. Request is for Sporanox or itraconazole capsules or oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole capsules or oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. 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;
5. Dose does not exceed (a or b):
   a. Capsules: 400 mg (4 capsules) per day;
   b. Oral solution: 200 mg (20 mL) per day.

Approval duration: 3 months

G. Coccidioidomycosis (off-label) (must meet all)**:**
1. Diagnosis of coccidioidomycosis infection, and member is infected with one of the following (a, b, or c):
   a. HIV-1, and member has peripheral blood CD4 < 250 cells/mm^3;
   b. Focal pulmonary disease;
   c. Disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis;
2. Request is for Sporanox or itraconazole capsules or oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole capsules or oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. Prescribed by or in consultation with an infectious disease specialist, pulmonologist, or HIV specialist;
5. Failure of fluconazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed one of the following (a, b, or c):
   a. For disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis (i or ii):
      i. Capsules: 600 mg (6 capsules) per day;
      ii. Oral solution: 600 mg (60 mL) per day;
   b. For coccidioidomycosis with HIV-1 co-infection (i or ii):
      i. Capsules: 600 mg (6 capsules) per day for the first three days, then 400 mg (4 capsules) per day thereafter;
      ii. Oral solution: 600 mg (60 mL) per day for the first three days, then 400 mg (40 mL) per day thereafter;
   c. For all other coccidioidomycosis infection (i or ii):
      i. Capsules: 400 mg (4 capsules) per day;
      ii. Oral solution: 400 mg (40 mL) per day.

Approval duration: 6 months

H. Sporotrichosis (off-label) (must meet all)**:**
1. Diagnosis of sporotrichosis infection, and member is infected with one of the following (a or b):
   a. Lymphocutaneous, cutaneous, non-severe pulmonary or osteoarticular sporotrichosis;
   b. Severe pulmonary, meningeal, or disseminated systemic sporotrichosis;
2. Request is for Sporanox or itraconazole capsules or oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole capsules or oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. Prescribed by or in consultation with an infectious disease specialist or pulmonologist;
5. For severe pulmonary, meningeal, or disseminated systemic sporotrichosis: Previous use of amphotericin B therapy, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed one of the following (a or b):
   a. Capsules: 400 mg (4 capsules) per day;
   b. Oral solution: 400 mg (40 mL) per day;

Approval duration: 12 months

I. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Onychomycosis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;

3. Request is for Sporanox or itraconazole capsules;
4. If request is for brand Sporanox, member must use generic itraconazole capsules, unless contraindicated or clinically significant adverse effects are experienced;
5. Member has not received more than 90 days of treatment;
6. If request is for a dose increase, new dose does not exceed 400 mg (4 capsules) per day.

Approval duration:
Fingernail disease: Up to 2 months of total treatment
Toenail disease: Up to 3 months of total treatment

B. Oropharyngeal/Esophageal Candidiasis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Request is for Sporanox or itraconazole oral solution;
4. If request is for brand Sporanox, member must use generic itraconazole oral solution, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, new dose does not exceed 200 mg (20 mL) per day.

Approval duration: 2 weeks

C. Blastomycosis, Histoplasmosis, or Aspergillosis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Request is for Sporanox or itraconazole capsules;
4. If request is for brand Sporanox, member must use generic itraconazole capsules, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, new dose does not exceed 400 mg (4 capsules) per day.

Approval duration:
Blastomycosis: 6 months
Histoplasmosis: 6 weeks
Aspergillosis: 3 months

D. Hematologic Malignancy (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Request is for Sporanox or itraconazole capsules or oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole capsules or oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. Member is responding positively to therapy;
5. If request is for a dose increase, new dose does not exceed (a or b):
   a. Capsules: 400 mg (4 capsules) per day;
   b. Oral solution: 200 mg (20 mL) per day.

Approval duration: 6 months

E. Coccidioidomycosis (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Request is for Sporanox or itraconazole capsules or oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole capsules or oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. If HIV-1 positive, member has peripheral blood CD4 < 250 cells/mm^3;
5. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. For disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis (i or ii):
      i. Capsules: 600 mg (6 capsules) per day;
      ii. Oral solution: 600 mg (60 mL) per day;

b. For all other coccidioidomycosis infections (i or ii):
   i. Capsules: 400 mg (4 capsules) per day;
   ii. Oral solution: 400 mg (40 mL) per day.

Approval duration: 12 months

F. Sporotrichosis (off-label) (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Request is for Sporanox or itraconazole capsules or oral solution;
3. If request is for brand Sporanox, member must use generic itraconazole capsules or oral solution, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Capsules: 400 mg (4 capsules) per day;
   b. Oral solution: 400 mg (40 mL) per day;

Approval duration: 12 months

G. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
CHF: congestive heart failure
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
terbinafine (Lamisil®)	250 mg PO once daily	500 mg per day
nystatin suspension	400,000 to 600,000 units (4 to 6 mL) per dose swished in the mouth 4 times per day	2.4 million units per day
clotrimazole troches/ lozenges (Mycelex®)	10 mg troche PO 5 times daily for 14 days	50 mg/day
fluconazole (Diflucan®)	400 mg PO per day	800 mg per day
voriconazole (Vfend®)	Weight ≥ 40 kg: 200 mg PO every 12 hours Weight < 40 kg: 100 mg PO every 12 hours	Weight ≥ 40 kg: 800 mg per day Weight < 40 kg: 400 mg per day
amphotericin B	Adults: 0.7 to 1 mg/kg/dose IV every 24 hours until favorable response. Continue step-down therapy with itraconazole to complete a total of at least 12 months of therapy	1 – 1.5 mg/kg/day IV

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

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): disopyramide, dronedarone, irinotecan, lurasidone, ivabradine, ranolazine, eplerenone, ticagrelor and, in subjects with varying degrees of renal or hepatic impairment, colchicine, fesoterodine, and solifenacin.
    - Sporanox capsules: telithromycin
    - Sporanox oral solution: isavuconazole, naloxegol, lomitapide, avanafil
  - Pregnancy, or women contemplating pregnancy
  - Hypersensitivity and anaphylaxis to itraconazole
- Boxed warning(s):
  - CHF or history of CHF (see contraindications)
  - Drug-drug interactions (see contraindications)

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Itraconazole (Sporanox) capsule	Blastomycosis	200 mg PO QD	400 mg/day
	Histoplasmosis	200 mg PO QD	400 mg/day
	Aspergillosis	200 to 400 mg PO QD	400 mg/day
	Onychomycosis	200 mg PO QD (toenails with or without fingernail involvement) 200 mg PO BID for 1 week, followed by no drug for 3 weeks, then another week of 200 mg PO BID or 200 mg PO QD for 6 weeks (fingernails only)	400 mg/day
	Coccidioidomycosis	200 mg PO BID or 200 mg BID-TID for nonmeningeal or meningeal coccidioidomycosis In patients co-infected with HIV: Adults: 200 mg PO TID for the first 3 days, then 200 mg PO BID Pediatrics: 5-10 mg/kg PO BID for the first 3 days, then 2-5 mg/kg PO BID	600 mg/day
	Lymphocutaneous or cutaneous sporotrichosis	200 mg PO QD for 3-6 months. If no response then increase to 200 mg PO BID.	400 mg/day
	Osteoarticular, pulmonary, meningeal, or disseminated systemic sporotrichosis	200 mg PO BID for at least 12 months	400 mg/day
Itraconazole (Sporanox) oral solution	Oropharyngeal candidiasis	200 mg (20 mL) PO 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

Drug Name	Indication	Dosing Regimen	Maximum Dose
	Coccidioidomycosis	200 mg (20 mL) PO BID or 200 mg (20 mL) BID-TID for nonmeningeal or meningeal coccidioidomycosis In patients co-infected with HIV: Adults: 200 mg PO TID for the first 3 days, then 200 mg PO BID Pediatrics: 5-10 mg/kg PO BID for the first 3 days, then 2-5 mg/kg PO BID	600 mg (60 mL)/day
	Lymphocutaneous or cutaneous sporotrichosis	200 mg (20 mL) PO QD for 3-6 months. If no response then increase to 200 mg PO BID.	400 mg (40 mL)/day
	Osteoarticular, pulmonary, meningeal, or disseminated systemic sporotrichosis	200 mg (20 mL) PO BID for at least 12 months	400 mg (40 mL)/day
	Esophageal candidiasis	100 mg (10 mL) PO daily for a minimum treatment of three weeks	200 mg (20 mL)/day

VI. Product Availability

- Capsule: 100 mg
- Oral solution: 10 mg/mL

VII. References

1. Sporanox Oral Solution Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020657s037lbl.pdf. Accessed January 26, 2022.
2. Sporanox Capsules Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc., March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020083s063lbl.pdf. Accessed January 26, 2022.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2022. Available at: http://www.clinicalpharmacology-ip.com/.
4. Chapman SW, Dismukes WE, Proia LA et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(12):1801.
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6. Wheat LJ, Freifeld AG, Kleiman MB et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45(7):807.
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8. Ameen M, Lear JT, Madan V, et al. British Association of Dermatologists' guidelines for the management of onychomycosis 2014. Br J Dermatology. 2014;171:937-58.
9. Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011 Feb 15;52(4):e56-93. doi: 10.1093/cid/cir073.

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11. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children.Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/whats-new. Updated January 24, 2022. Accessed January 26, 2022.
12. Kauffman C, Bustamante B, Chapman S, et al. Clinical Practice Guidelines for the Management of Sporotrichosis: 2007 Update by the Infectious Diseases Society of America. 2007; 45:1255-65.
13. Fungal Diseases: Sporotrichosis. Centers for Disease Control and Prevention. Last updated: November 13, 2019. Accessed January 26, 2022.
14. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clinical Infectious Diseases. 2016; 63(6): e112–e146.
15. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. J Clin Oncol. 2018; 36(30): 3043-3054.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2018 annual review: added age where appropriate; replaced trial of amphotericin B with 3 month trial of voriconazole for aspergillosis per IDSA; removed drug interaction contraindication; references reviewed and updated.	02.06.18	05.18
2Q 2019 annual review: no significant changes; removed age requirement due to lack of age restriction in guidelines; added oral solution dosing to hematologic malignancy indication; corrected dosing typo in continued therapy section for blastomycosis, histoplasmosis, and aspergillosis; references reviewed and updated.	02.26.19	05.19
2Q 2020 annual review: added criteria for coccidioidomycosis infection (off-label); references reviewed and updated.	04.07.20	05.20
Added criteria for sporotrichosis infection (off-label); revised all requests for Sporanox capsules or oral solution to require medical justification that supports inability to use generic itraconazole capsules or oral solution; updated Appendix B; references reviewed and updated.	05.21.20	08.20
2Q 2021 annual review: no significant changes; removed Onmel from policy since it is no longer available (MediSpan obsolete date of August 2020); clarified the specific agents that should be used if the preferred generic is unable to be used; “medical justification” revised to “must use” language; references reviewed and updated.	01.12.21	05.21
2Q 2022 annual review: no significant changes; updated max dosing for coccidioidomycosis infection per compendia, including addition of HIV-specific dosing; references reviewed and updated.	01.26.22	05.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.