

## **Clinical Policy: Itraconazole (Sporanox, Onmel, Tolsura)**

Reference Number: CP.PMN.124

Effective Date: 11.01.06

Last Review Date: 05.20

Line of Business: Commercial, HIM\*, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### **Description**

Itraconazole (Sporanox<sup>®</sup>, Onmel<sup>®</sup>, Tolsura<sup>®</sup>) is an azole antifungal agent.

*\*For Health Insurance Marketplace (HIM), if request is through pharmacy benefit, Onmel and brand Sporanox capsule are non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

### **FDA Approved Indication(s)**

Onmel is indicated for the treatment of onychomycosis of the toenail caused by *Trichophyton rubrum* or *T. mentagrophytes*.

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 indicated 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.

Limitation(s) of use: Tolsura is not indicated for the treatment of onychomycosis. Tolsura is not interchangeable or substitutable with other itraconazole products.

### **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.*

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that Onmel, Sporanox, and Tolsura are **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 capsules or Onmel tablets (toenails only);
3. 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;
4. Dose does not exceed (a or b):
  - a. Sporanox capsules: 400 mg (4 capsules) per day;
  - b. Onmel tablets: 200 mg (1 tablet) per day.

**Approval duration:**

**Medicaid/Commercial** – Fingernail disease: 2 months; toenail disease: 3 months

**HIM** – Fingernail disease: 2 months; toenail disease: 3 months for generic Sporanox  
(refer to HIM.PA.103 for Onmel and brand Sporanox)

**B. Oropharyngeal Candidiasis (must meet all):**

1. Diagnosis of oropharyngeal candidiasis;
2. Request is for Sporanox oral solution;
3. Failure of a 14-day trial of nystatin suspension or clotrimazole troches/lozenges, unless clinically significant adverse effects are experienced or both are contraindicated;
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: 4 weeks**

**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: 4 weeks**

**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;  
*\*Prior authorization may be required for voriconazole*
4. For Tolsura requests, medical justification supports inability to use generic itraconazole capsules (e.g., contraindications to the excipients);

5. Dose does not exceed one of the following (a or b):
  - a. Sporanox: 400 mg (4 capsules) per day;
  - b. Tolsura: 260 mg (4 capsules) per day.

**Approval duration:**

**Medicaid/Commercial** – 3 months

**HIM** – 3 months for Tolsura and generic Sporanox (*refer to HIM.PA.103 for brand Sporanax*)

**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, medical justification supports inability to use generic itraconazole capsules (e.g., contraindications to the excipients);
4. Dose does not exceed one of the following (a or b):
  - a. Sporanox: 400 mg (4 capsules) per day;
  - b. Tolsura: 260 mg (4 capsules) per day.

**Approval duration:**

**Medicaid/Commercial** – Blastomycosis: 6 months; Histoplasmosis: 6 weeks

**HIM** – Blastomycosis: 6 months; Histoplasmosis: 6 weeks for Tolsura and generic Sporanax (*refer to HIM.PA.103 for brand Sporanax*)

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

1. Diagnosis of hematologic malignancy;
2. Request is for Sporanox or Tolsura;
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. For Tolsura requests, medical justification supports inability to use generic itraconazole capsules (e.g., contraindications to the excipients);
5. Dose does not exceed one of the following (a, b, or c):
  - a. Sporanox capsules: 400 mg (4 capsules) per day;
  - b. Sporanox oral solution: 200 mg (20 mL) per day;
  - c. Tolsura: 260 mg (4 capsules) per day.

**Approval duration:**

**Medicaid/Commercial** – 3 months

**HIM** – 3 months for Tolsura, oral solution, and generic capsules (*refer to HIM.PA.103 for brand Sporanax capsules*)

**G. Coccidioidomycosis (off-label) (must meet all):**

1. Diagnosis of coccidioidomycosis infection and meets one of the following (a, b, or c):
  - a. Member is infected with HIV-1 and has peripheral blood CD4 < 250 cells/mm<sup>3</sup>;
  - b. Member is infected with focal pulmonary disease;
  - c. Member is infected with disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis;

2. Request is for Sporanox;
3. Prescribed by or in consultation with an infectious disease, pulmonary specialist, or HIV specialist;
4. Failure of fluconazole, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed one of the following (a, b, c, or d):
  - a. For disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis: Sporanox capsules: 800 mg (8 capsules) per day;
  - b. For disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis: Sporanox oral solution: 800 mg (80 mL) per day;
  - c. For all other coccidioidomycosis infection: Sporanox capsules: 400 mg (4 capsules) per day;
  - d. For all other coccidioidomycosis infection: Sporanox oral solution: 400 mg (40 mL) per day;

**Approval duration:**

**Medicaid/Commercial** – 6 months

**HIM** – 6 months for generic Sporanox (*refer to HIM.PA.103 for brand Sporanox*)

**H. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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 (a or b):
  - a. Sporanox capsules: 400 mg (4 capsules) per day;
  - b. Onmel tablets: 200 mg (1 tablet) per day.

**Approval duration:**

**Medicaid/Commercial** - Fingernail disease: up to 2 months total; toenail disease: up to 3 months total

**HIM** - Fingernail disease: up to 2 months total; toenail disease: up to 3 months total for generic Sporanox (*refer to HIM.PA.103 for Onmel and brand Sporanox*)

**B. Oropharyngeal/Esophageal Candidiasis (must meet all):**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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: 2 weeks**

**C. Blastomycosis, Histoplasmosis, or Aspergillosis (must meet all):**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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 (4 capsules) per day;
  - b. Tolsura: 260 mg (4 capsules) per day.

**Approval duration:**

**Medicaid/Commercial** – Blastomycosis: 6 months; Histoplasmosis: 6 weeks; Aspergillosis: 3 months

**HIM** – Blastomycosis: 6 months; Histoplasmosis: 6 weeks; Aspergillosis: 3 months for Tolsura and generic Sporanox (*refer to HIM.PA.103 for brand Sporanox*)

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Request for Sporanox or Tolsura;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):
  - a. Sporanox capsules: 400 mg (4 capsules) per day;
  - b. Sporanox oral solution: 200 mg (20 mL) per day;
  - c. Tolsura: 260 mg (4 capsules) per day.

**Approval duration:**

**Medicaid/Commercial** – 6 months

**HIM** – 6 months for Tolsura, oral solution, and generic capsules (*refer to HIM.PA.103 for brand Sporanox capsules*)

**E. Coccidioidomycosis (off-label) (must meet all):**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Request is for Sporanox;
3. If HIV-1 positive: peripheral blood CD4 < 250 cells/mm<sup>3</sup>;
4. Dose does not exceed one of the following (a, b, c, or d):
  - a. For disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis: Sporanox capsules: 800 mg (8 capsules) per day;
  - b. For disseminated extrathoracic nonmeningeal or meningeal coccidioidomycosis: Sporanox oral solution: 800 mg (80 mL) per day;
  - c. For all other coccidioidomycosis infection: Sporanox capsules: 400 mg (4 capsules) per day;
  - d. For all other coccidioidomycosis infection: Sporanox oral solution: 400 mg (40 mL) per day;

**Approval duration:**

**Medicaid/Commercial** – 12 months

**HIM** – 12 months for generic Sporanox (*refer to HIM.PA.103 for brand Sporanox*)

**F. Other diagnoses/indications** (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less);** or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

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 for all relevant lines of business and may require prior authorization.*

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

*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), Tolsura: 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, Tolsura: 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)<br><br>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   | 600 mg/day         |
|                                       | In life-threatening situations | Loading dose of 200 mg PO TID given for the first 3 days of treatment  | 600 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       |
|------------------------|-------------------------------|---|--------------------|
|                        | Esophageal candidiasis        | 100 mg (10 mL) PO daily for a minimum treatment of three weeks  | 200 mg (20 mL)/day |
|                        | Coccidioidomycosis            | 200 mg (20 mL) PO BID or 200 mg (20 mL) BID- TID for nonmeningeal or meningeal coccidioidomycosis   | 600 mg/day         |
| Itraconazole (Onmel)   | Onychomycosis                 | Toenail: 200 mg (one tablet) PO QD for 12 consecutive weeks   | 200 mg/day         |
| Itraconazole (Tolsura) | Blastomycosis, histoplasmosis | 130 mg PO QD. 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 PO QD or BID   | 260 mg/day         |

## VI. Product Availability

| Drug Name               | Availability                                |
|-------------------------|---|
| Itraconazole (Sporanox) | Capsules: 100 mg<br>Oral solution: 10 mg/mL |
| Itraconazole (Onmel)    | Tablets: 200 mg                             |
| Itraconazole (Tolsura)  | Capsules: 65 mg                             |

## VII. References

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14. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_o.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_o.pdf). Accessed 04.05.20

| Reviews, Revisions, and Approvals  | Date  | P&T Approval Date |
|--|-------|-------------------|
| Updated references. Clarified “other” to be other FDA labeled indications in criteria for approval.  | 04.15 | 04.15             |
| Removed onychomycosis requirement of pathologic (KOH prep, fungal culture, or nail biopsy) and approval requirement of only 84 capsules, added age requirement and maximum dose;<br>For Oropharyngeal/Esophageal Candidiasis added age requirement, request for oral solution and maximum dose;<br>For Blastomycosis, Histoplasmosis or Aspergillosis added age requirement, maximum dose and increased continued approval from 14 days to 6 months;<br>Removed Other FDA Labeled Indications;<br>Revised background information to clearly include indications and MOA; | 02.16 | 05.16             |

| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| References updated and added.  |          |                   |
| <p>Added 6 week trial of terbinafine for fingernails and 12 week trial of terbinafine for toenail onychomycosis and limited trial to one course instead of 2 courses.</p> <p>Removed requirement of multiple toes and/or fingers involved or member having a diagnosis of diabetes mellitus, peripheral vascular disease, or is immunocompromised for onychomycosis per specialist feedback.</p> <p>Separated approval durations for onychomycosis for ingernails only: 2 months and toenails: 3 months per PI, guideline and clinical pharmacology.</p> <p>Separated initial criteria for oropharyngeal and esophageal candidiasis. Esophageal candidiasis requires a trial of fluconazole only per IDSA guidelines.</p> <p>Added 14 day duration of nystatin or clotrimazole trial and fluconazole trial for oropharyngeal candidiasis per IDSA guideline.</p> <p>Added 21 day duration of fluconazole trial for esophageal candidiasis per IDSA guideline.</p> <p>Changed approval duration from 8 weeks to 4 weeks for oropharyngeal and esophageal candidiasis per IDSA guideline and PI.</p> <p>Changed continued approval duration for oropharyngeal and esophageal candidiasis from 8 weeks to 2 weeks per IDSA guideline and PI.</p> <p>Added Request is for Sporanox capsules for onychomycosis, blastomycosis, histoplasmosis, and aspergillosis.</p> <p>Clarified continued approval duration for blastomycosis, histoplasmosis, and aspergillosis per IDSA guidelines.</p> <p>Added continued approval criteria for onychomycosis.</p> <p>Converted to new template</p> <p>Removed age criteria as age is not an absolute contraindication per FDA labeling</p> <p>Updated references</p> | 03.17    | 05.17             |
| 2Q 2018 annual review: policies combined for Medicaid, Commercial, and HIM; added Onmel to policy; added age; added 3 months trial of voriconazole for aspergillosis per IDSA; added criteria for hematologic malignancy; 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; corrected dosing typo in continued therapy section for blastomycosis, histoplasmosis, and aspergillosis; references reviewed and updated.   | 02.26.19 | 05.19             |

| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| For blastomycosis, histoplasmosis, aspergillosis, and hematologic malignancy added Tolsura to criteria requiring medical justification that supports inability to use generic itraconazole capsules per SDC and prior clinical guidance. | 12.02.19 |                   |
| 2Q 2020 annual review: added criteria for Coccidioidomycosis infection (off-label); references reviewed and updated.   | 04.07.20 | 05.20             |

### **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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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