Clinical Policy: Itraconazole (Onmel, Sporanox)
Reference Number: ERX.NPA.25
Effective Date: 06.01.15
Last Review Date: 05.19

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

Description
Itraconazole (Onmel®, Sporanox®) is an azole antifungal agent

FDA Approved Indication(s)
Onmel is indicated for the treatment of onychomycosis of the toenail caused by Trichophyton rubrum or T. mentagrophytes.

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 Onmel and Sporanox 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:
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 a 14-day trial of nystatin suspension or clotrimazole troches/lozenges unless contraindicated or clinically significant adverse effects are experienced;
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 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. 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 capsules;
3. 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;
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 dose unless contraindicated or clinically significant adverse effects are experienced;
4. 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. 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. Member has not received more than 90 days of treatment;
4. If request is for a dose increase, new dose does not exceed:
   a. Sporanox capsules: 400 mg (4 capsules) per day;
   b. Onmel tablets: 200 mg (1 tablet) 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 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 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 capsules;
4. 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;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed (a or b):
   1. Sporanox capsules: 400 mg (4 capsules) per day
   2. Sporanox oral solution: 200 mg (20 mL) per day.

Approval duration: 6 months

E. 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
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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>terbinafine (Lamisil®)</td>
<td>250 mg PO once daily</td>
<td>500 mg per day</td>
</tr>
<tr>
<td>nystatin suspension</td>
<td>400,000 to 600,000 units (4 to 6 mL) per dose swished in the mouth 4 times per day</td>
<td>2.4 million units per day</td>
</tr>
<tr>
<td>clotrimazole troches/lozenges (Mycelex®)</td>
<td>10 mg troche PO 5 times daily for 14 days</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>fluconazole (Diflucan®)</td>
<td>400 mg PO per day</td>
<td>800 mg per day</td>
</tr>
<tr>
<td>voriconazole (Vfend®)</td>
<td>Weight ≥ 40 kg: 200 mg PO every 12 hours</td>
<td>Weight ≥ 40 kg: 800 mg per day</td>
</tr>
<tr>
<td></td>
<td>Weight &lt; 40 kg: 100 mg PO every 12 hours</td>
<td>Weight &lt; 40 kg: 400 mg per day</td>
</tr>
</tbody>
</table>

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 to itraconazole

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

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole (Sporanox)</td>
<td>Blastomycosis</td>
<td>200 mg PO QD</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>capsule</td>
<td>Histoplasmosis</td>
<td>200 mg PO QD</td>
<td>400 mg/day</td>
</tr>
<tr>
<td></td>
<td>Aspergillosis</td>
<td>200 mg PO QD</td>
<td>400 mg/day</td>
</tr>
<tr>
<td></td>
<td>Onychomycosis</td>
<td>200 mg PO QD (toenails with or without fingernail involvement)</td>
<td>400 mg/day</td>
</tr>
<tr>
<td></td>
<td>In life-threatening situations</td>
<td>Loading dose of 200 mg PO TID given for the first 3 days of treatment</td>
<td>600 mg/day</td>
</tr>
</tbody>
</table>

In life-threatening situations:
Loading dose of 200 mg PO TID given for the first 3 days of treatment

Drug Name: Itraconazole

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### Drug Name | Indication | Dosing Regimen | Maximum Dose
---|---|---|---
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
 | Esophageal candidiasis | 100 mg (10 mL) PO daily for a minimum treatment of three weeks | 200 mg (20 mL)/day
Itraconazole (Onmel) | Onychomycosis | Toenail: 200 mg (one tablet) PO QD for 12 consecutive weeks | 200 mg/day

### VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
</table>
| Itraconazole (Sporanox) | Capsules: 100 mg  
Oral solution: 10 mg/mL |
| Itraconazole (Onmel) | Tablets: 200 mg |

### VII. References

## Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Details</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created.</td>
<td>06.15</td>
<td>06.15</td>
</tr>
<tr>
<td>Updated to new template (converted algorithm to bulleted criteria, added background and references). Separated criteria by diagnosis. Removed safety criteria (&quot;Previously used Onmel safely&quot;) as this is outside the scope of a PBM. Modified requirement of fluconazole trial duration from ≥ 3 weeks to ≥ 2 weeks in treatment of candidiasis per literature review. Modified approval duration of candidiasis prophylaxis in setting of hematologic malignancy from 4 weeks to 3 months to match aspergillosis prophylaxis approval duration per literature review; removed trial duration of fluconazole for candidiasis prophylaxis as duration of fluconazole therapy is moot (failure would mean infection at any point while on prophylaxis therapy). Added requirement for trial/failure of amphotericin B in treatment of aspergillosis per FDA labeling.</td>
<td>07.16</td>
<td>09.16</td>
</tr>
<tr>
<td>Converted to new template. Removed requirement of generic trial of itraconazole for onychomycosis; Removed “If request is for Onmel, failure of generic itraconazole capsules, unless contraindicated” for candidiasis because Onmel is only approved for onychomycosis; changed 14 day trial to 21 day duration of fluconazole trial for esophageal candidiasis per IDSA guideline; Removed lab results dated within the past 14 days are consistent with diagnosis for blastomycosis, histoplasmosis and aspergillosis; Added DDIs per black box warning that such interactions can be fatal; Separated continued approval criteria. Updated approval durations to be in line with current IDSA guidelines. Separated toenail and finger nail durations per IDSA. Changed Aspergillosis, Blastomycosis, and Histoplasmosis approval duration from 6 months per IDSA.</td>
<td>06.17</td>
<td>08.17</td>
</tr>
<tr>
<td>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.</td>
<td>02.06.18</td>
<td>05.18</td>
</tr>
<tr>
<td>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.</td>
<td>02.26.19</td>
<td>05.19</td>
</tr>
</tbody>
</table>

### 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.

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