### Antifungal Agents -
ciclopirox, efinaconazole, itraconazole, tavaborole, terbinafine

**Prior Authorization with Quantity Limit Program Summary**

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Indication(s)</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jublia®</strong> (efinaconazole)</td>
<td>The topical treatment of onychomycosis of the toenail(s) due to Trichophyton rubrum and Trichophyton mentagrophytes</td>
<td>Apply to affected toenails once daily for 48 weeks</td>
</tr>
<tr>
<td>topical solution</td>
<td></td>
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</tr>
<tr>
<td><strong>Kerydin®</strong> (tavaborole)a</td>
<td>The topical treatment of onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes.</td>
<td>Apply to affected toenails once daily for 48 weeks</td>
</tr>
<tr>
<td>topical solution</td>
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<tr>
<td><strong>Lamisil®</strong> (terbinafine)a</td>
<td>The treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)</td>
<td>Onychomycosis - 250 mg daily Fingernail – treat 6 weeks Toenail – treat 12 weeks</td>
</tr>
<tr>
<td>tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Onmel®</strong> (itraconazole)</td>
<td>The treatment of onychomycosis of the toenail caused by Trichophyton rubrum or T. mentagrophytes</td>
<td>Onychomycosis toenail-200 mg once daily for 12 weeks</td>
</tr>
<tr>
<td>tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Penlac®</strong> (ciclopirox)a</td>
<td>The treatment of onychomycosis of the toenail or fingernail (topical treatment in immunocompetent patients with mild to moderate onychomycosis without lunula involvement, due to Trichophyton rubrum)</td>
<td>Apply daily to affected area</td>
</tr>
<tr>
<td>topical solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>FDA Indication(s)</td>
<td>Dosing</td>
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<tr>
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</tr>
<tr>
<td><strong>Sporanox®</strong>&lt;sup&gt;a&lt;/sup&gt; (itraconazole)&lt;br&gt;capsules, oral solution</td>
<td>The treatment of blastomycosis, histoplasmosis, aspergillosis, onychomycosis of the toenail or fingernail&lt;br&gt;The treatment of oropharyngeal and esophageal candidiasis</td>
<td><strong>Blastomycosis</strong>-200 mg daily (up to 400 mg daily if 200 mg not effective)&lt;br&gt;<strong>Histoplasmosis</strong>-200 mg daily (up to 400 mg daily if 200 mg not effective)&lt;br&gt;<strong>Aspergillosis</strong>-200-400 mg daily&lt;br&gt;<strong>Onychomycosis toenail</strong>-200 mg daily for 12 weeks&lt;br&gt;<strong>Onychomycosis fingernail</strong>-200 mg twice daily for 1 week, then 3 weeks off, then 200 mg twice daily for 1 more week&lt;br&gt;<strong>Candidiasis</strong>-100 mg daily for a minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg per day may be used based on medical judgement of the patient’s response to therapy</td>
</tr>
<tr>
<td><strong>Tolsura™</strong> (itraconazole)&lt;br&gt;capsules</td>
<td>The treatment of blastomycosis, histoplasmosis, and aspergillosis (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. Tolsura is not interchangeable or substitutable with other itraconazole products</td>
<td><strong>Blastomycosis and histoplasmosis</strong>-130 mg to 260 mg daily&lt;br&gt;<strong>Aspergillosis</strong>-130 mg to 260 mg daily</td>
</tr>
</tbody>
</table>

**CLINICAL RATIONALE**

**Esophageal candidiasis and candidemia**
Infectious Diseases Society of America (IDSA) guidelines recommend an echinocandin as the first line therapy for candidemia in non-neutropenic patients, with fluconazole as an alternative. Fluconazole is first-line therapy for esophageal candidiasis. Fluconazole is also recommended for prophylaxis against esophageal candidiasis in at risk patients. For patients with fluconazole-refractory disease, guidelines recommend itraconazole or voriconazole. Up to 80% of patients with fluconazole refractory esophageal candidiasis will respond to itraconazole.<sup>4</sup>

**Blastomycosis and histoplasmosis**
Itraconazole is the recommended therapy for the treatment of chronic cavity pulmonary histoplasmosis. Other forms of histoplasmosis are generally treated with amphotericin B.<sup>5</sup> IDSA guidelines recommend itraconazole as the first line oral agent for the treatment of mild to moderate blastomycosis. Itraconazole is also recommended in patients as a step down from amphotericin B for more severe cases of blastomycosis. Fluconazole and voriconazole are considered alternatives for the treatment of blastomycosis.<sup>6</sup>

**Onychomycosis (Tinea unguium)**
Onychomycosis typically causes no symptoms other than an undesirable appearance of the nail. Guidelines recommend consideration of treatment if walking is uncomfortable, abnormal looking nails are causing significant psychological distress, or if the patient has diabetes, vascular disease, or a connective tissue disorder. Treatment may be necessary if the nail infection is the source of a fungal skin infection or if the person is, or may become, severely immunocompromised.11

Onychomycosis can be difficult to distinguish from other causes of nail dystrophy and because of slow nail growth (six months for fingernails and twelve months for toenails) evidence of treatment failure may not be apparent for several months or more. If the diagnosis is not confirmed and improvement does not occur, it is impossible to ascertain if treatment failure has occurred or if the initial diagnosis was incorrect. Guidelines on the treatment of fungal and candidal infections of the nail recommend laboratory confirmation and nail specimens for diagnosis before initiation of treatment.11

The British Association of Dermatologists guidelines for the management of onychomycosis recommends both itraconazole and terbinafine as first line treatments for dermatophyte onychomycosis and generally prefer terbinafine over itraconazole.15 The American Academy of Family Physicians recommends terbinafine as first-line treatment for dermatophyte onychomycosis due to its tolerability, high cure rate, and low cost. A meta-analysis showed a mycotic cure rate of 76% for the use of terbinafine for systemic treatment of onychomycosis.11 Several meta-analyses have found oral terbinafine more effective than oral itraconazole for onychomycosis.7-10 The guidelines consider oral fluconazole as an alternative (off-label use).

Topical agents are recommended for patients who cannot take oral antifungals and in those with less than 50% of the distal nail affected and no lunular involvement.11 Ciclopirox is considered less effective than systemic therapy, but has no systemic side effects or drug interactions. Additionally, a comparative study showed combination of ciclopirox and oral terbinafine had a higher mycotic cure rate and complete cure rate compared to terbinafine alone.11 The prescribing information for Penlac indicates it is part of a comprehensive management program that includes removal of the unattached, infected nails as frequently as monthly, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures.3

**Safety**

Onmel, Sporanox capsules, Sporanox solution, and Tolsura all carry a black box warning against their administration for the treatment of onychomycosis in patients with evidence of ventricular dysfunction. The warnings also list several drugs that are contraindicated with the use of these antifungals. See individual prescribing information for more information.1, 12, 16, 17

**REFERENCES**

Itraconazole, Terbinafine Prior Authorization with Quantity Limit

TARGET AGENTS

- Lamisil® (terbinafine)\textsuperscript{ab}
- Onmel™ (itraconazole)
- Sporanox® (itraconazole)\textsuperscript{b}
- Tolsura™ (itraconazole)

\textit{a} - Lamisil cream and spray are not included in the program
\textit{b} - available as a generic; generic designated target for QL only

PROGRAM PRIOR AUTHORIZATION AND QUANTITY LIMITS

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamisil (terbinafine)</td>
<td>11000080100310</td>
<td>M, N, O, or Y</td>
<td>1 tablet/day</td>
</tr>
<tr>
<td>250 mg tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onmel (itraconazole)</td>
<td>11407035000330</td>
<td>M, N, O, or Y</td>
<td>1 tablet/day</td>
</tr>
<tr>
<td>200 mg tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporanox (itraconazole)</td>
<td>11407035000120</td>
<td>M, N, O, or Y</td>
<td>4 capsules/day</td>
</tr>
<tr>
<td>100 mg capsule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg/mL oral solution</td>
<td>11407035002020</td>
<td>M, N, O, or Y</td>
<td>40 mL/day</td>
</tr>
<tr>
<td>Tolsura (itraconazole)</td>
<td>11407035000113</td>
<td>M, N, O, or Y</td>
<td>4 capsules/day</td>
</tr>
<tr>
<td>65 mg capsule</td>
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</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Target Agents will be approved when ALL of the following are met:

1. ONE of the following:
   a. The patient has an FDA approved diagnosis other than onychomycosis (tinea unguium) for the requested agent
   \textbf{OR}
   b. The patient has a diagnosis of onychomycosis (tinea unguium) AND ALL of the following:
      i. The patient has not received treatment for onychomycosis with the requested agent in the past 12 months
      \textbf{AND}
      ii. The patient has ONE of the following: diabetes mellitus, peripheral vascular insufficiency, immune deficiency due to medical condition or treatment (e.g. cancer chemotherapy, HIV/AIDS, anti-rejection therapy post organ transplant), pain limiting normal activity, or secondary bacterial infection in the surrounding skin or systemic dermatosis with impaired skin integrity
      \textbf{AND}
      iii. Treatment of the patient’s onychomycosis (tinea unguium) is medically necessary and not entirely for cosmetic reasons
      \textbf{AND}
      iv. Fungal nail infection is confirmed by laboratory testing (KOH preparation, fungal culture or nail biopsy)
      \textbf{AND}
      v. If the requested agent is a brand agent, ONE of the following:
         1. The patient’s medication history includes use of a generic antifungal onychomycosis agent (e.g. itraconazole, terbinafine, ciclopirox) in the past 999 days
         \textbf{OR}
         2. The patient has an intolerance or hypersensitivity to a generic antifungal onychomycosis agent
         \textbf{OR}
3. The patient has an FDA labeled contraindication to ALL generic antifungal onychomycosis agents
   **OR**
4. BOTH of the following:
   a. The prescriber has stated that the patient has tried a generic antifungal onychomycosis agent
   **AND**
   b. A generic antifungal onychomycosis agent was discontinued due to lack of effectiveness or an adverse event
   **OR**
5. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   **AND**
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   **AND**
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm
   **OR**
6. The prescriber has provided documentation that ALL generic antifungal onychomycosis agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

   **AND**
2. The patient does NOT have any FDA labeled contraindications to the requested agent
   **AND**
3. ONE of the following:
   a. The requested quantity (dose) does NOT exceed the program quantity limit
   **OR**
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      **AND**
      ii. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication
      **AND**
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
   **OR**
   c. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      **AND**
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
      **AND**
      iii. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

**Length of approval for onychomycosis***
Lamisil/terbinafine: 6 weeks for fingernail infection, 12 weeks for toenail infection
Sporanox capsules/itraconazole capsules: Fingernail infection: 5 weeks (2 treatment pulses, each consisting of one week of therapy separated by a 3-week period) Toenails with or without fingernail involvement: 12 weeks
Onmel/itraconazole: 12 weeks for toenail fungal infection

*Lamisil/Tolsura/terbinafine and Sporanox/Onmel/itraconazole are limited to one approval per 12 month period for onychomycosis (tinea unguium)

**Length of approval for FDA approved diagnosis other than onychomycosis:**
Lamisil or terbinafine: 6 weeks for tinea capitis or other FDA approved indications
Sporanox or itraconazole solution: 6 weeks for oropharyngeal or esophageal candidiasis
Sporanox or itraconazole capsules: 12 months for other FDA approved indications
Onmel/itraconazole: 12 months for other FDA approved indications
Tolsura/itraconazole: 12 months for other FDA approved indications
Ciclopirox, Efinaconazole, Tavaborole Prior Authorization with Quantity Limit

TARGET AGENTS

- **Jublia** (efinaconazole 10% topical solution)
- **Kerydin** (tavaborole 5% topical solution)
- **Penlac** (ciclopirox 8% topical solution)

a - available as a generic; generic only targeted for quantity limit

PROGRAM PRIOR AUTHORIZATION AND QUANTITY LIMITS

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
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</tr>
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<tbody>
<tr>
<td>Jublia (efinaconazole)</td>
<td>90154037002020</td>
<td>M, N, O, or Y</td>
<td>4 mL / 30 days</td>
</tr>
<tr>
<td>topical solution 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kerydin (tavaborole)a</td>
<td>90156080002010</td>
<td>M, N, O, or Y</td>
<td>4 mL / 30 days</td>
</tr>
<tr>
<td>topical solution 5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penlac (ciclopirox)a</td>
<td>90150030002020</td>
<td>M, N, O, or Y</td>
<td>6.6 mL / 30 days</td>
</tr>
<tr>
<td>topical solution 8%</td>
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</tbody>
</table>

a - available as a generic

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

**Jublia** (efinaconazole), **Kerydin** (tavaborole), or **Penlac** (ciclopirox) will be approved when ALL of the following are met:

1. The patient has a diagnosis of onychomycosis (tinea unguium)
   AND
2. The patient has ONE of the following: diabetes mellitus, peripheral vascular insufficiency, immune deficiency due to medical condition or treatment (e.g. cancer chemotherapy, HIV/AIDS, anti-rejection therapy post organ transplant), pain limiting normal activity, or secondary bacterial infection in the surrounding skin or systemic dermatosis with impaired skin integrity
   AND
3. Treatment of the patient’s onychomycosis (tinea unguium) is medically necessary and not entirely for cosmetic reasons
   AND
4. The fungal nail infection is confirmed by laboratory testing (KOH preparation, fungal culture or nail biopsy)
   AND
5. ONE of the following:
   a. The patient has tried and had an inadequate response to an oral antifungal agent
   OR
   b. The patient has an intolerance or hypersensitivity to an oral antifungal agent
   OR
   c. The patient has an FDA labeled contraindication to ALL oral antifungal agents
   OR
   d. The prescriber has provided information that an oral antifungal agent is not clinically appropriate
   OR
   e. The patient is currently being treated with the requested agent as indicated by ALL of the following:
      i. A statement by the prescriber that the patient is currently taking the requested agent
      AND
ii. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent

AND

iii. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

f. The prescriber has provided documentation that ALL oral antifungal agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

AND

6. If the requested agent is Penlac, ciclopirox 8% topical solution; treatment will include removal of the unattached, infected nail(s) by an appropriate health care professional

AND

7. If the requested agent is a brand agent, ONE of the following:

a. The patient’s medication history includes use of a generic antifungal onychomycosis agent (e.g., itraconazole, terbinafine, ciclopirox) in the past 999 days

OR

b. The patient has an intolerance or hypersensitivity to a generic antifungal onychomycosis agent

OR

c. The patient has an FDA labeled contraindication to ALL generic antifungal onychomycosis agents

OR

d. BOTH of the following:

i. The prescriber has stated that the patient has tried a generic antifungal onychomycosis agent

AND

ii. A generic antifungal onychomycosis agent was discontinued due to lack of effectiveness or an adverse event

OR

e. The patient is currently being treated with the requested agent as indicated by ALL of the following:

i. A statement by the prescriber that the patient is currently taking the requested agent

AND

ii. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent

AND

iii. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

f. The prescriber has provided documentation that ALL generic antifungal onychomycosis agents cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

AND

8. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

9. ONE of the following:

a. The requested quantity (dose) does NOT exceed than the program quantity limit

OR
b. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit AND
   ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose AND
   iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

OR

c. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit AND
   ii. The requested quantity (dose) is greater than the maximum FDA labeled dose AND
   iii. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

Length of approval: 12 months
### FDA Contraindication(s)

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Contraindication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jublia (efinaconazole)</td>
<td>None</td>
</tr>
<tr>
<td>Kerydin (tavaborole)</td>
<td>None</td>
</tr>
<tr>
<td>Lamisil (terbinafine)</td>
<td>Individuals with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis.</td>
</tr>
<tr>
<td>Onmel (itraconazole)</td>
<td>Do not administer for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. Do not administer for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy. Coadministration of cisapride, dofetilide, ergot alkaloids such as dihydroergotamine, ergotamine, ergometrine (ergonovine), and methylergometrine (methylergonovine), felodipine, levacetylmethadol (levomethadyl), lovastatin, methadone, oral midazolam, nisoldipine, pimozide, quinidine, simvastatin, and triazolam with Onmel is contraindicated. Anaphylaxis and hypersensitivity have been reported with use of itraconazole. Onmel is contraindicated in patients who have shown hypersensitivity to itraconazole products.</td>
</tr>
<tr>
<td>Penlac (ciclopirox)</td>
<td>Contraindicated in individuals who have shown hypersensitivity to any of its components</td>
</tr>
<tr>
<td>Sporanox (itraconazole)</td>
<td>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.</td>
</tr>
<tr>
<td>Tolsura (itraconazole)</td>
<td>Tolsura can cause or exacerbate congestive heart failure. If signs or symptoms of CHF occur or worsen during administration of Tolsura, reassess the benefit-risk of continuing treatment. Co-administration of certain drugs that either affect metabolism of itraconazole or whose metabolism is affected by itraconazole.</td>
</tr>
</tbody>
</table>