Topical Antifungals, itraconazole, terbinafine Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, 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.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
1/1/2024	8/1/2017

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
ciclopirox Topical solution	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*)		3
Jublia® (efinaconazole) Topical solution	The topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*		13
Kerydin® (tavaborole) Topical solution	The topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*	Available as a generic; designated target as determined by client	14
Sporanox® (itraconazole) Capsules Oral solution	The treatment of blastomycosis, histoplasmosis, aspergillosis, onychomycosis of the toenail or fingernail The treatment of oropharyngeal and esophageal candidiasis	Available as a generic; designated target as determined by client	1
terbinafine Tablets	The treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)		2
Tolsura® (itraconazole) Capsules	The treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients: • Blastomycosis, pulmonary and extrapulmonary • Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis		16

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Aspergillosis, pulmonary and extrapulmonary, 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		

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Esophageal candidiasis and candidemia	Infectious Diseases Society of America (IDSA) guidelines recommend fluconazole as the first line oral therapy for esophageal candidiasis and candidemia in nonneutropenic patients. Fluconazole is also recommended for prophylaxis against esophageal candidiasis in at risk patients. For patients with fluconazole-refractory disease, guidelines recommend itraconazole or voriconazole. Voriconazole has demonstrated effectiveness for both mucosal and invasive candidiasis, but offers little advantage over fluconazole as initial therapy. Its clinical use has been primarily for step-down oral therapy in patients with infection due to *C. krusei* and fluconazole-resistant, voriconazole-susceptible *C. glabrata*.(4)
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.(5) 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.(6)
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 ciclopirox 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	Sporanox capsules, Sporanox solution and Tolsura all carry a black box warning warning against their administration for the treatment of onychomycosis in patients with evidence of ventricular dysfunction. 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.(1,16,17) Terbinafine carries the following contraindication: • Individuals with a history of allergic reaction to oral terbinafine because of the risk of anaphylaxis. Ciclopirox carries the following contraindication: • Contraindicated in individuals who have shown hypersensitivity to any of its components Sporanox carries the following contraindication: • 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. Tolsura carries the following contraindications: • Co-administration of certain drugs that either affect metabolism of itraconazole or whose metabolism is affected by itraconazole. • Hypersensitivity to itraconazole

REFERENCES

Number	Reference
1	Sporanox prescribing information. Janssen Pharmaceutical Companies. March 2019.
2	Lamisil prescribing information. Novartis Pharmaceuticals Corporation. March 2019.
3	Penlac prescribing information. Sanofi Aventis. June 2016.
4	Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016;62:e1-e50.
5	Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Disease Society of America. *Clin Infec Dis*. 2009;48:503-535.
6	Wheat LJ, Freifeld AG, Lkeiman 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;45:807-25.
7	Criber BJ et al. Long-term efficacy of antifungals in toenail onychomycosis: a critical review. *British Journal of Dermatology*. 2001;145:446-52.
8	Haugh M et al. Terbinafine in fungal infections of the nails: a meta-analysis of randomized clinical trials. *British Journal of Dermatology.* 2002;147:118-121.
9	Epstein E. How often does oral treatment of toenail onychomycosis produce a disease-free nail. *Arch Dermatol.* 1999;134:1551-4.

Number	Reference
10	Crawford F et al. Oral treatments for toenail onychomycosis. *Arch Dermatol.* 2002;138:811-6.
11	Westerberg, Dyanne, DO and Voyack, Michael DO. Onychomycosis: Current Trends in Diagnosis and Treatment. *Am Fam* Physician. 2013; 88 (11):762-770.
12	~~Onmel prescribing information. Merz Pharmaceuticals, LLC. November 2012.~~ Reference no longer used.
13	Jublia prescribing information. Bausch Health Companies, Inc. March 2022.
14	Kerydin prescribing information. Pfizer Inc. August 2018.
15	Ameen M, Lear JT, Madan V, Mustapa MFM, M. Richardson. British Association of Dermatologists' guidelines for the management of onychomycosis 2014. *Br J Dermatol* 2014; 171: 937-58.
16	Tolsura prescribing information. Mayne Pharma. December 2018.
17	Sporanox oral solution prescribing information. Janssen Pharmaceuticals, Inc. March 2019.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Itraconazole, Terbinafine Prior Authorization with Quantity Limit						
Sporanox ; Sporanox pulsepak ; Tolsura	itraconazole cap	100 MG ; 65 MG	M ; N ; O	N ; O ; Y		
Sporanox	itraconazole oral soln	10 MG/ML	M ; N ; O	O ; Y		
	terbinafine hcl tab	250 MG	M ; N ; O	Y		
Ciclopirox, Efinaconazole, Tavaborole Prior Authorization with Quantity Limit						
Ciclodan	ciclopirox solution	8 %	M ; N ; O	Y		
Jublia	efinaconazole soln	10 %	M ; N ; O	N		
Kerydin	tavaborole soln	5 %	M ; N ; O	O ; Y		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
	Terbinafine HCl Tab 250 MG	250 MG	30	Tablets	30	DAYS			
Ciclodan	Ciclopirox Solution 8%	8 %	6.6	mLs	30	DAYS			
Jublia	Efinaconazole Soln 10%	10 %	4	mLs	30	DAYS			
Kerydin	Tavaborole Soln 5%	5 %	4	mLs	30	DAYS			
Sporanox	Itraconazole Oral Soln 10 MG/ML	10 MG/ML	1200	mLs	30	DAYS			
Sporanox ; Sporanox pulsepak	Itraconazole Cap 100 MG	100 MG	120	Capsules	30	DAYS			
Tolsura	Itraconazole Cap 65 MG	65 MG	120	Capsules	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	terbinafine hcl tab	250 MG	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ciclodan	ciclopirox solution	8 %	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jublia	efinaconazole soln	10 %	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Kerydin	tavaborole soln	5 %	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Sporanox	itraconazole oral soln	10 MG/ML	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Sporanox ; Sporanox pulsepak ; Tolsura	itraconazole cap	100 MG ; 65 MG	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	Terbinafine HCl Tab 250 MG	250 MG	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Ciclodan	Ciclopirox Solution 8%	8 %	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Jublia	Efinaconazole Soln 10%	10 %	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Kerydin	Tavaborole Soln 5%	5 %	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Sporanox	Itraconazole Oral Soln 10 MG/ML	10 MG/ML	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Sporanox ; Sporanox pulsepak	Itraconazole Cap 100 MG	100 MG	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Tolsura	Itraconazole Cap 65 MG	65 MG	FlexRx Closed ; FlexRx Open ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
CiclopiroxEfinaconazoleTavaborole	**Julia (efinaconazole), Kerydin (tavaborole), or 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: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. 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 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:

Module	Clinical Criteria for Approval
	1. The prescriber has stated that the patient has tried a generic antifungal onychomycosis agent **AND** 2. 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: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. 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 **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
ItraconazoleTerbinafine	**Sporanox (itraconazole), Tolsura (itraconazole) or terbinafine** 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 **OR** B. The patient has a diagnosis of onychomycosis (tinea unguium) AND ALL of the following: 1. The patient has not received treatment for onychomycosis with the requested agent in the past 12 months **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. Fungal nail infection is confirmed by laboratory testing (KOH preparation, fungal culture or nail biopsy) **AND** 5. 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: 1. The prescriber has stated that the patient has tried a generic antifungal onychomycosis agent **AND** 2. 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: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND**

Module	Clinical Criteria for Approval
	2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. 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** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of approval for onychomycosis*:** terbinafine — Fingernail infection: 6 weeks — Toenail infection: 12 weeks Sporanox (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 *Tolsura, terbinafine and Sporanox (itraconazole) are limited to one approval per 12 month period for onychomycosis (tinea unguium) **Length of approval for FDA approved diagnosis other than onychomycosis:** terbinafine — Tinea capitis or other FDA approved indications: 6 weeks Sporanox (itraconazole) capsules — Other FDA approved indications: 12 months Sporanox (itraconazole) solution — Oropharyngeal or esophageal candidiasis: 6 weeks Tolsura — Other FDA approved indications: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Ciclopirox Efinaco	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed than the program quantity limit **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>nazoleTavaborole</td><td>2. ALL of the following:
A. The requested quantity (dose) exceeds the program quantity limit AND
B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose AND
C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit OR
3. ALL of the following:
A. The requested quantity (dose) exceeds the program quantity limit AND
B. The requested quantity (dose) exceeds the maximum FDA labeled dose AND
C. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months</td></tr>
<tr><td>ItraconazoleTerbinafine</td><td>Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met:

1. The requested quantity (dose) does NOT exceed the program quantity limit OR
2. ALL of the following:
A. The requested quantity (dose) exceeds the program quantity limit AND
B. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication AND
C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit OR
3. ALL of the following:
A. The requested quantity (dose) exceeds the program quantity limit AND
B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication AND
C. The prescriber has submitted information in support of therapy with a higher dose for the requested indication

Length of Approval for onychomycosis*

<table>
<tr><td>terbinafine</td><td>Fingernail infection:

6 weeks</td><td>Toenail infection:

12 weeks</td></tr>
<tr><td>Sporanox (itraconazole) capsules</td><td>Fingernail infection:

5 weeks

(2 treatment pulses, each consisting of one week of therapy separated by a 3-week period)</td><td>Toenails with or without fingernail involvement:

12 weeks</td></tr>
</table>
*Tolsura, terbinafine and Sporanox (itraconazole) are limited to one approval per 12 month period for onychomycosis (tinea unguium)

Length of Approval for FDA approved diagnosis other than onychomycosis:

<table>
<tr><td>terbinafine</td><td>Tinea capitis or other FDA approved indications:

6 weeks</td></tr>
</table></td></tr>
</table>

Module	Clinical Criteria for Approval	
	Sporanox (itraconazole) capsules	Other FDA approved indications: 12 months
	Sporanox (itraconazole) solution	Oropharyngeal or esophageal candidiasis: 6 weeks
	Tolsura	Other FDA approved indications: 12 months