BlueCross BlueShield of Alabama

Antifungal Agents - ciclopirox, efinaconazole, tavaborole
Prior Authorization with Quantity Limit
Program Summary

This prior authorization applies to Commercial, GenPlus, SourceRx, and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the Ciclopirox, Efinaconazole, tavaborole Prior Authorization (PA) program is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical trials and to discourage cosmetic utilization. The PA defines appropriate use as confirmed fungal nail infections that are considered medically necessary to treat and cannot be treated with an oral antifungal agent. The program requires the trial of a generic antifungal onychomycosis agent or that the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least one generic antifungal onychomycosis agent. Approval will not be granted to patients who have any FDA labeled contraindication(s) to the requested agent. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis. Requests will be reviewed when patient specific documentation is provided.

TARGET AGENTS

Julia (efinaconazole 10% topical solution)
Kerydin (tavaborole 5% topical solution)
Penlac (ciclopirox 8% topical solution)[a]

a - available as a generic; designated target as determined by client

PROGRAM PRIOR AUTHORIZATION AND QUANTITY LIMITS

Brand (generic)	GPI	Quantity Per Day (Or As Noted)	Multisource Code
Julia (efinaconazole)			
topical solution 10%	90154037002020	4 mL / 30 days	M, N, O, or Y
Kerydin (tavaborale)			
topical solution 5%	90156080002010	4 mL / 30 days	M, N, O, or Y
Penlac (ciclopirox)			
topical solution 8%[a]	90150030002020	6.6 mL / 30 days	M, N, O, or Y

a - available as a generic; designated target as determined by client

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

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

1. The patient does not have any FDA labeled contraindication(s) to the requested agent
   AND
2. The patient has a diagnosis of onychomycosis (tinea unguium)
   AND
3. 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

4. Treatment of the patient's onychomycosis (tinea unguium) is medically necessary and not entirely for cosmetic reasons
   AND
5. The fungal nail infection is confirmed by laboratory testing (KOH preparation, fungal culture or nail biopsy)
   AND
6. The patient has a treatment failure with, a contraindication to an oral antifungal agent, or the prescriber has provided documentation that an oral antifungal agent is not clinically appropriate
   AND
7. 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
8. 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 90 days
      OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least one generic antifungal onychomycosis agent

   AND
9. ONE Of the following:
   a. The requested quantity (dose) is NOT greater 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) is less than or equal to the 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 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 FDA labeled dose
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of approval: 12 months

FDA APPROVED INDICATIONS AND DOSAGE[1-3,16-19]

Agent	FDA Indication(s)	Dosing
Jublia® (efinaconazole) topical solution	Onychomycosis of the toenails due to Trichophyton rubrum and Trichophyton mentagrophytes	Apply to affected toenail once daily for 48 weeks
Kerydin® (tavaborole) topical solution	Onychomycosis of the toenails due to Trichophyton rubrum or Trichophyton mentagrophytes.	Apply to affected toenail once daily for 48 weeks
Lamisil® (terbinafine) tablets, oral granules	Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium) Tinea capitis	**Onychomycosis -** 250 mg daily **Fingernail –** treat 6 weeks **Toenail –** treat 12 weeks **Tinea capitis** – 125 mg -250 mg daily for 6 weeks (see table) *Dosage by body weight:* <table><tr><td><25 kg</td><td>125 mg/day</td></tr><tr><td>25-35 kg</td><td>187.5 mg/day</td></tr><tr><td>>35 kg</td><td>250 mg/day</td></tr></table>
Onmel® (itraconazole) tablets	Onychomycosis of the toenail caused by *Trichophyton rubrum* or *T. mentagrophytes*	**Onychomycosis toenail-**200 mg once daily for 12 weeks
Penlac® (ciclopirox) topical solution	Onychomycosis of the toenail or fingernail (topical treatment in immunocompetent patients with mild to moderate onychomycosis without lunula involvement, due to *Trichophyton rubrum*)	Apply daily to affected area
Sporanox® (itraconazole) capsules, oral solution	Blastomycosis, histoplasmosis, aspergillosis, onychomycosis of the toenail or fingernail	**Blastomycosis-**200 mg daily (up to 400 mg daily if 200 mg not effective) **Histoplasmosis-**200 mg daily (up to 400 mg daily if 200 mg not effective) **Aspergillosis-**200-400 mg daily **Onychomycosis toenail-**200 mg daily for 12 weeks **Onychomycosis fingernail-**200 mg twice daily for 1 week, then 3 weeks off, then 200 mg twice daily for 1 more week

CLINICAL RATIONALE

Esophageal candidiasis and candidemia[4]

Infectious Diseases Society of America (IDSA) guidelines recommend oral fluconazole as the first line therapy for candidemia in non neutropenic patients and 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.

Blastomycosis and histoplasmosis[5,6]

Itraconazole is the recommended therapy for the treatment of chronic cavity pulmonary histoplasmosis. Other forms of histoplasmosis are generally treated with amphotericin B. 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.

Onychomycosis (Tinea unguium)
Onychomycosis typically causes no symptoms other than an undesirable appearance of the nail.[15] 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.[15]

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 specimans for diagnosis before initiation of treatment.[15]

The British Association of Dermatologists guidelines for the management of onychomycosis recommended both itraconazole and terbinafine as first line treatments for dermatophyte onychomycosis and generally prefer terbinafine over itraconazole.[20] 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.[15] Several meta-analyses have found oral terbinafine more effective than oral itraconazole for onychomycosis.[8-11] 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. [15] Ciclopirox is considered less effective than systemic therapy, but has no systemic side effects or drug interactions.Additionally, a comparative study showed combination of ciclopririox and oral terbinafine had a higher mycotic cure rate and complete cure rate compared to terbinafine alone.[15] 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]

Tinea capitis
The guidelines for the management of tinea capitis in children from the European Society for Pediatric Dermatology note that terbinafine, itraconazole, and fluconazole appear to have efficacy rate and potential adverse effects similar to those of griseofulvin in children with tinea capitis caused by the *Trichophyton* species. Griseofulvin is the treatment of choice for cases caused by *Microsporum* species.[13] A Cochrane review found that terbinafine for 4 weeks and griseofulvin for 8 weeks have demonstrated similar efficacy in three studies.[14] Two comparative trials of terbinafine oral granules vs. griseofulvin in patients 4 to 12 years of age demonstrated superior rates of complete cure for terbinafine compared to griseofulvin.[14,16]

A meta-analysis evaluated efficacy between griseofulvin and terbinafine in the treatment of tinea capitis infections. The review did not show a significant difference in the overally efficacy of the two drugs but specific efficacy differences were observed based on the infectious species. For tinea capitis caused by *Microsporum* spp., griseofulvin is superior ($p = 0.04$), whereas

terbinafine is superior for *Trichophyton* spp. infection (p = 0.04). These results support species-specific differences in treatment efficacy between griseofulvin and terbinafine.

REFERENCES

1. Sporanox prescribing information. Janssen Pharmaceutical Companies. March 2017.
2. Lamisil prescribing information. Novartis Pharmaceuticals Corporation. January 2017.
3. Penlac prescribing information. Sanofi Aventis. July 2006.
4. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503-35.
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. Roberts DT et al. Guidelines for treatment of onychomycosis. *British Journal of Dermatology.* 2003;148:402-10.
8. Criber BJ et al. Long-term efficacy of antifungals in toenail onychomycosis: a critical review. *British Journal of Dermatology*. 2001;145:446-52.
9. 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.
10. Epstein E. How often does oral treatment of toenail onychomycosis produce a disease-free nail. *Arch Dermatol.* 1999;134:1551-4.
11. Crawford F et al. Oral treatments for toenail onychomycosis. *Arch Dermatol.* 2002;138:811-6.
12. Kakourou T, Uksal. Guidelines for the management of tinea capitis in children. *Pediatric Dermatology* 2010; 27: 226-228.
13. Gonzalez U, Seaton T, Bergus G et al. Systemic antifungal therapy for tinea capitis in children. *Cochrane Data Syst Reviews.* 2007;4:CD004685.
14. Elewski BE, Caceres HW, DeLeon L, et al. Terbinafine hydrochloride oral granules versus oral griseofulvin suspension in children with tinea capitis. Results of 2 randomized, investigator-blinded, multicenter, international, controlled trials. *J Am Acad Dermatol.* 2008;59(1):41-54.
15. Westerberg, Dyanne, DO and Voyack, Michael DO. Onychomycosis: Current Trends in Diagnosis and Treatment. *Am Fam* Physician. 2013; 88 (11):762-770.
16. Lamisil oral granules prescribing information. Novartis Pharmaceuticals Corporation. January 2017.
17. Onmel prescribing information. Sebela Pharmaceuticals. November 2012.
18. Jublia prescribing information. Valeant Pharmaceuticals North America, LLC. September 2016.
19. Kerydin prescribing information. Anacor Pharmaceuticals, Inc. March 2015.
20. 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.

to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.