

**Regence BlueCross BlueShield of Oregon • Regence BlueShield  
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**Medication Policy Manual**

**Policy No:** dru070

**Topic:** Penlac<sup>®</sup>, ciclopirox nail lacquer

**Date of Origin:** May 20, 1997

**Revised/Effective Date:** July 17, 2009

**Next Review Date:** July 2010

**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Ciclopirox (Penlac<sup>®</sup>) nail lacquer is a topical medication used to treat fungal infections of the fingernails and toenails.

## **Policy/Criteria**

- I.** Most contracts require prior authorization approval of ciclopirox prior to coverage. Ciclopirox may be considered medically necessary for the treatment of onychomycosis when the patient has one of the following conditions A through H and supported by clinical documentation:
  - A.** Diabetes.
  - B.** Immunocompromised host (e.g., HIV).
  - C.** Peripheral neuropathy.
  - D.** Peripheral circulatory disorders.
  - E.** History of significant cellulitis (requiring systemic antibiotic therapy) secondary to onychomycosis.
  - F.** Recurring ingrown nails (secondary to the onychomycosis) requiring surgical repair or removal.
  - G.** Fingernail involvement with paronychia.
  - H.** Other functional impairment from onychomycosis that affects performing normal daily activities.
  
- II.** Administration, Quantity Limitations, and Authorization Period
  - A.** Regence considers ciclopirox nail lacquer to be a self-administered medication.
  - B.** When prior authorization is approved, ciclopirox may be authorized in quantities of one prescribed treatment course up to 12 months.
  - C.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
  
- III.** Ciclopirox is considered not medically necessary when used for all other conditions, including, but not limited to, concurrent therapy with oral antifungal therapy.

## Position Statement

### *Background*

- Onychomycosis (fungal infection of the fingernails or toenails) is a relatively common and relapsing condition in the adult population.
- In certain cases, treatment of onychomycosis is considered a cosmetic issue.
- Coverage for treatment of onychomycosis is dependent on the individual member's plan and subject to language defined by the member's contract.
- Reinforcement of general personal hygiene (such as wearing cotton socks and non-occlusive shoes and keeping nails trimmed) is considered a primary treatment in the management and prevention of onychomycosis. <sup>[28-30]</sup>
- In some instances, onychomycosis may be debilitating or require medical intervention. <sup>[29-30]</sup>
- Treatment of onychomycosis may be considered of potential clinical benefit when the condition is associated with comorbid conditions, or when onychomycosis is part of a more serious pathology or results in a functional impairment. <sup>[30]</sup>
- Antifungal agents used to treat onychomycosis include terbinafine, itraconazole, and ciclopirox nail lacquer.
- Griseofulvin is no longer considered a drug of choice due to its low cure rates, high relapse rates, and relatively long duration of therapy (up to 1 year) necessary. <sup>[22]</sup>

### *Clinical Efficacy*

#### ONYCHOMYCHOSIS

- Although onychomycosis typically affects multiple nails, clinical trials have been generally limited to assessing efficacy of antifungal agents in 1 target nail. <sup>[1-5,10-11, 25-27]</sup>
- When comparing efficacy among antifungal agents, differences in study design need to be considered and definition of measured endpoints reported.

### *Mycological Cure*

- There are no clinical trials comparing oral antifungal agents to topical products. However, oral antifungal therapy (terbinafine, itraconazole) appears to achieve higher mycological cures (defined as negative KOH microscopy and negative culture) than topical ciclopirox. [2,4,5,10]
- One meta-analysis of all U.S. and non-U.S. published literature reports the following mycologic cure rates. [27] (A higher rate of mycological cure with ciclopirox is reported than those found in U.S. trials). [25-27]
  - \* Griseofulvin 41.1% (95% C.I. 1.2-81.0).
  - \* Itraconazole continuous 66.3% (95% C.I. 58.1 - 74.6).
  - \* Itraconazole (pulse) 70.8% (95% C.I. 59.6-82.1).
  - \* Terbinafine 77.2 (95% C.I. 69.3-85.1).
  - \* Ciclopirox 52.6% (95% C.I. 44.4-60.7) vs. U.S. trials: 29%-36% [25-26]

### *Clinical Cure*

Varying definitions used in studies to define "clinical cure" (such as % nail plate affected) lead to a wide disparity of reported "clinical" efficacy among these antifungal agents. [2,4,20]

- \* Clinical trials using terbinafine or itraconazole have reported "clinical" cure rates for toenail onychomycosis ranging from 35% [20] to more than 80%. [2, 4]

### *Disease-free nail/Complete Cure Rate*

- An analysis of published data reported that the ability of terbinafine and itraconazole in achieving a disease-free nail (defined as clinically normal nail plus negative results of KOH microscopy and culture). [19]
  - \* Standard courses of terbinafine achieved a disease-free nail in approximately 35% to 50% of patients after 12-32 weeks of continuous or pulse dose therapy. [19]
  - \* Itraconazole produced a disease-free nail rate of approximately 25% to 40% after 12-16 weeks of continuous or pulse dose therapy. [19]
- Topical ciclopirox demonstrates a lower "complete cure" rate (defined as a clear nail and negative mycology) of 5.5%-8.5% in patients with onychomycosis after 48 weeks (12 months) of treatment. [25]

- In the majority of comparative trials, terbinafine has been more effective than itraconazole in the treating onychomycosis, [2, 4-5, 10-11] whereas two studies have shown similar efficacy. [10, 21] Two trials comparing pulsed itraconazole with pulsed terbinafine showed similar efficacy between the two regimens, although both trials had significant flaws. [31,32]
- Treatment of toenail onychomycosis with terbinafine plus aggressive debridement was compared to treatment with terbinafine alone in 504 patients with moderate-to-severe dermatophyte infections. At the end of study (week 48), only the difference in clinical cure rates reached statistical significance (terbinafine + debridement 59.8% vs. terbinafine alone, 51.4%, P = 0.023). [39]
  - \* A *post-hoc* analysis in patients aged > 65 years from the same trial resulted in similar results. [40]
  - \* Another analysis from the same trial reported that terbinafine + aggressive debridement resulted in improved treatment satisfaction and reduced symptom frequency. [41]
- There is some data to suggest that terbinafine pulse therapy (daily therapy 1 week a month) may be as effective and a less costly alternative to daily therapy. [4,10-11] However, two double-blind, randomized trials suggest that continuous terbinafine treatment is superior to pulsed therapy, dosed either 500 mg daily, 1 week per month for 3 months, or 350 mg daily, 2 weeks per month for 3 months. [33, 34]
- One small randomized, single-blind trial found pulse itraconazole (200 mg daily for one week per month) equivalent to continuous terbinafine (250 mg daily for 12 weeks) as measured by rates of mycological cure at 1 year. [38]
- One open-label, single-blind, randomized trial compared combination therapy with ciclopirox nail lacquer plus oral terbinafine with oral terbinafine alone in patients with confirmed onychomycosis. This small trial (N=73) found no significant benefit in combining these agents. [35]

#### *Long-term Outcomes*

- There is no evidence that assesses treatment outcomes with itraconazole, terbinafine or ciclopirox in relation to improvements in functional impairment, such as pain or ability to walk or decrease in pain.
- Pharmacoeconomic analysis suggests that ciclopirox may be a less costly alternative, when considering extra medical costs associated with lab tests and adverse effects with oral therapy. [27]
- A more favorable side-effect profile for ciclopirox may provide a benefit in patients that have an increased risk for systemic side effects or drug-drug interactions.
- Studies evaluating frequency of relapse are in some cases of short duration.

- \* Itraconazole -- One study reported recurrent nail dystrophy of 17% and mycological failure rate of 55% at 2 years after treatment. <sup>[20]</sup>
- \* Terbinafine -- Relapse rate for terbinafine is approximately 11-18% <sup>[1, 23-24]</sup> at up to 12 to 21 months after treatment. <sup>[1, 23-24]</sup>
- \* Ciclopirox -- Reported average relapse rate is 20.7% at up to 6 months following discontinuation. <sup>[26]</sup>

### *Safety*

- The use of systemic itraconazole and terbinafine is limited by their risk for potential side effects and need to be weighed against the risk/benefit ratio in using other therapeutic alternatives.
- On May 9, 2001, the U.S. Food and Drug Administration (FDA) issued a public health advisory concerning serious risks associated with the use of Sporanox<sup>®</sup> (itraconazole) and Lamisil<sup>®</sup> (terbinafine): <sup>[18]</sup>
  - \* A Black Box Warning has been issued for Sporanox: <sup>[37]</sup>
  - \* Congestive Heart Failure such that "Sporanox (itraconazole) capsules 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. Drug Interactions: Coadministration of cisapride, pimozone, quinidine, or dofetilide with Sporanox is contraindicated."
  - \* A warning was issued for Lamisil: <sup>[36]</sup>

Rare cases of liver failure, some leading to death or liver transplant, have occurred with the use of Lamisil Tablets for the treatment of onychomycosis in individuals with and without pre-existing liver disease. In the majority of liver cases reported in association with Lamisil use, the patients had serious underlying systemic conditions and an uncertain causal relationship with Lamisil. Although ongoing post-marketing surveillance and clinical trials have shown no increase in the frequency of these adverse events reported, it is important to reinforce the need for proper patient selection when considering treatment with Lamisil Tablets.
- Ciclopirox nail lacquer has a more favorable side effect profile that may be of benefit when there is increased risk for systemic side effects or drug-drug interactions with oral therapy.

## References

1. Drake LA et al. "Oral terbinafine in the treatment of toenail onychomycosis: North American multicenter trial." *J Am Acad Dermatol* 1997;37(5):740-5.
2. Brautigam M et al. "Terbinafine versus itraconazole: a controlled clinical comparison in onychomycosis of the toenails." *J Am Acad Dermatol* 1998;38(5):PS053-PS056.
3. Haneke E et al. "Safety and efficacy of intermittent therapy with itraconazole in finger- and toenail onychomycosis: a multicentre trial." *Mycoses* 1998; 41: 521-527.
4. Tosti A et al. "Treatment of dermatophyte nail infections: An open randomized study comparing intermittent terbinafine therapy with continuous terbinafine treatment and intermittent itraconazole therapy." *J Am Acad Dermatol* 1996;34(4):595-600.
5. De Backer M et al. "Twelve weeks of continuous oral therapy for toenail onychomycosis caused by dermatophytes: a double-blind comparative trial of terbinafine 250mg/day versus itraconazole 200mg/day." *J Am Acad Dermatol* 1998;38(5):PS057-PS062.
6. Drake LA et al. "The impact of onychomycosis on quality of life: Development of an international onychomycosis-specific questionnaire to measure patient quality of life." *J Am Acad Dermatol* 1999;41(2):198-96.
7. Drake LA et al. "The effect of onychomycosis on quality of life." *J Am Acad Dermatol* 1998;38(5):702-704.
8. Rich P. "Nail disorders: diagnosis and treatment of infectious, inflammatory, and neoplastic nail conditions." *Med Clin North Am* 1998; 82(5): P1171-82.
9. Scher RK. "Novel treatment strategies for superficial mycoses." *J Am Acad Dermatol* 1999;40(6):S21-6.
10. Gupta AK et al. "Single-blind, randomized, prospective study on terbinafine and itraconazole for treatment of dermatophyte toenail onychomycosis in the elderly." *J Am Acad Dermatol* 2001;44:479-84.
11. Gupta AK et al. "Single-blind, randomized, prospective study of sequential itraconazole and terbinafine pulse compared with terbinafine pulse for the treatment of toenail onychomycosis." *J Am Acad Dermatol* 2001;44(3):485-91.
12. Hay RJ. "Therapeutic potential of terbinafine in subcutaneous and systemic mycoses." *Br J Dermatol* 1999;56:36-40.
13. Leshner JL et al. "Oral therapy of common superficial fungal infections of the skin." *J Am Acad Dermatol* 1999;40(6 Pt 2):S31-4.

14. Barnetson RS et al. "Comparison of one week of oral terbinafine (250mg/day) with four weeks of treatment with clotrimazole 1% cream in interdigital tinea pedis." *Br J Dermatol* 1998;139(4):675-8.
15. Tausch I et al. "Short-term itraconazole versus terbinafine in the treatment of tinea pedis or manus." *Int J Dermatol* 1998;37(2):140-2.
16. Caceres-Rios H et al. "Comparison of terbinafine and griseofulvin in the treatment of tinea capitis." *J Am Acad Dermatol* 2000;42(1 Pt 1):80-4.
17. Jahangir M et al. "A double-blind, randomized, comparative trial of itraconazole versus terbinafine for 2 weeks in tinea capitis." *Br J Dermatol* 1998;139(4):672-4.
18. <http://www.fda.gov/cder/drug/advisory/sporanox-lamisil/default.htm>
19. Epsteine E. "How often does oral treatment of toenail onychomycosis produce a disease-free nail? An analysis of published data." *Arch Dermatol* 1998;134:1551-4.
20. Heikkila A, Stubb S. "Long-term results of patients with onychomycosis treated with itraconazole." *Acta Derm Venereol* 1997;77:70-71.
21. Arenas R et al. "Open randomized comparison of itraconazole versus terbinafine in onychomycosis." *Int J Dermatol* 1993;34:138-143.
22. Zaias N et al. "Diagnosing and treating onychomycosis." *J Fam Pract* 1996;42:513-8.
23. Gupta K, Shear N. "Terbinafine: an update." *J Am Acad Dermatol* 1997;37:979-88.
24. Villars V, Jones T. "Special features of the clinical use of oral terbinafine in the treatment of fungal diseases." *Br J Dermatol* 1992;126(suppl 39):61-9.
25. Penlac<sup>®</sup> [package insert]. Berwyn, PA: Dermik Laboratories.; July 2006.
26. Gupta AK et al. "Ciclopirox nail lacquer topical solution 8% in the treatment of toe onychomycosis." *J Am Acad Dermatol* 2000;43(4):S70-S80.
27. Gupta AK. "Pharmacoeconomic analysis of ciclopirox nail lacquer solution 8% and the new oral antifungal agents used to treat dermatophyte toe onychomycosis in the United States." *J Am Acad Dermatol* 2000;43:S81-S95.
28. Neale D., Adams, IM. *Common Foot Disorders* (3rd ed.). Edinburgh: Churchill Livingstone, 1989.
29. Rodgers P et al. "Treating Onychomycosis." *Am Fam Physician* 2001;63:663-72, 677-8.
30. Drake LA et al. "Guidelines of care for superficial mycotic infections of the skin: onychomycosis." *J Am Acad Dermatol* 1996;34(1):116-21.

31. Mishra M, Panda P, Tripathy S, Sengupta S, Mishra K. An open randomized comparative study of oral itraconazole pulse and terbinafine pulse in the treatment of onychomycosis. *Indian J Dermatol Venereol Leprol.* 2005 Jul-Aug;71(4):262-6.
32. Warshaw EM, Nelson D, Carver SM, Zielke GR, Webster N, Lederle FA, et. al. A pilot evaluation of pulse itraconazole vs. terbinafine for treatment of Candida toenail onychomycosis. *Int J Dermatol.* 2005 Sep;44(9):785-8.
33. Warshaw EM, Fett DD, Bloomfield HE, Grill JP, Nelson DB, Quintero V, et. al. Pulse versus continuous terbinafine for onychomycosis: a randomized, double-blind, controlled trial. *J Am Acad Dermatol.* 2005 Oct;53(4):578-84.
34. Sigurgeirsson B, Elewski BE, Rich PA, Opper C, Cai B, Nyirady J, et.al. Intermittent versus continuous terbinafine in the treatment of toenail onychomycosis: a randomized, double-blind comparison. *J Dermatolog Treat.* 2006;17(1):38-44.
35. Gupta AK; Onychomycosis Combination Therapy Study Group. Ciclopirox topical solution, 8% combined with oral terbinafine to treat onychomycosis: a randomized, evaluator-blinded study. *J Drugs Dermatol.* 2005 Jul-Aug;4(4):481-5.
36. Lamisil [package insert]. East Hanover, NJ.:Novartis Pharmaceuticals Company; November 2005
37. Sporanox [package insert]. Titusville, NJ.: Janssen Pharmaceutica Products; April 2008
38. Gupta AK, Gover MD, Lynde CW. Pulse itraconazole vs. continuous terbinafine for the treatment of dermatophyte toenail onychomycosis in patients with diabetes mellitus. *J Eur Acad Dermatol Venereol.* 2006 Nov;20(10):1188-93.
39. Jennings MB, Pollak R, Harkless LB, Kianifard F, Tavakkol A. Treatment of toenail onychomycosis with oral terbinafine plus aggressive debridement: IRON-CLAD, a large, randomized, open-label, multicenter trial. *J Am Podiatr Med Assoc.* 2006 Nov-Dec;96(6):465-73.
40. Tavakkol A, Fellman S, Kianifard F. Safety and efficacy of oral terbinafine in the treatment of onychomycosis: analysis of the elderly subgroup in Improving Results in ONychomycosis-Concomitant Lamisil and Debridement (IRON-CLAD), an open-label, randomized trial. *Am J Geriatr Pharmacother.* 2006 Mar;4(1):1-13.
41. Potter LP, Mathias SD, Raut M, Kianifard F, Landsman A, Tavakkol A. The impact of aggressive debridement used as an adjunct therapy with terbinafine on perceptions of patients undergoing treatment for toenail onychomycosis. *J Dermatolog Treat.* 2007;18(1):46-52.
42. Oren I, Rowe JM, Sprecher H, Tamir A, Benyamini N, Akria L, et. al. A prospective randomized trial of itraconazole vs fluconazole for the prevention of fungal infections in patients with acute leukemia and hematopoietic stem cell transplant recipients. *Bone Marrow Transplant.* 2006 Jul;38(2):127-34.

43. Ito Y, Ohyashiki K, Yoshida I, Takeuchi M, Aoyama Y, Mugitani A, et. al. The prophylactic effect of itraconazole capsules and fluconazole capsules for systemic fungal infections in patients with acute myeloid leukemia and myelodysplastic syndromes: a Japanese multicenter randomized, controlled study. *Int J Hematol.* 2007 Feb;85(2):121-7.

Cross References
Lamisil <sup>®</sup> , terbinafine dru065
Sporanox <sup>®</sup> , itraconazole dru066

Codes	Number	Description
N/A		