



# CIGNA PHARMACY COVERAGE POLICY

This Coverage Policy should NOT be used for Great-West benefit plans.

**Subject Oral Onychomycosis Antifungal Therapy: [Terbinafine (Lamisil®), Itraconazole (Sporanox®)]**

**Effective Date ..... 12/15/2008**  
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**Coverage Policy Number ..... 4007**

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## Hyperlink to Related Coverage Positions

Ciclopirox (Penlac® Nail Lacquer)

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Policy

**CIGNA HealthCare covers onychomycosis antifungal therapy [terbinafine (Lamisil®), itraconazole (Sporanox®)] for treatment of onychomycosis if the patient is diabetic or immunocompromised due to a disease or medical condition (i.e., cancer, HIV/AIDS, organ or bone marrow transplant recipient).**

**If patient is not diabetic or immunocompromised, CIGNA HealthCare covers onychomycosis antifungal therapy [terbinafine (Lamisil®), itraconazole (Sporanox®)] as medically necessary when the following indications are met:**

- for treatment of onychomycosis **AND** when **ALL** of the following are met:
  - diagnosis of fungal infection must be confirmed by either a positive potassium hydroxide (KOH) stain, para-aminosalicylic acid (PAS) stain, positive dermatophyte testing medium (DTM) or positive fungal culture
  - oral onychomycosis therapy has not been used as treatment within the past 32 weeks
  - **AND ONE** of the following:
    - patient experiences pain, limiting normal activity
    - patient has significant peripheral vascular compromise

**Note:** Coverage approval will extend to 12 weeks of therapy for toenail onychomycosis and six weeks for fingernail onychomycosis. CIGNA allows PULSE DOSING with itraconazole (Sporanox®) ONLY. There is a maximum of TWO pulses for fingernails and THREE pulses for toenails.

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## General Background

### FDA Approved Indications

Lamisil (terbinafine hydrochloride) oral granules are indicated for the treatment of tinea capitis in patients 4 years of age and older.

Sporanox (itraconazole) capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: blastomycosis, pulmonary and extrapulmonary; histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis; and aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy. Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained before therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly. Sporanox capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients: onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (*tinea unguium*); and onychomycosis of the fingernail due to dermatophytes (*tinea unguium*). Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

Onychomycosis is an infection of the fingernails and toenails caused by dermatophytes, yeast, and molds. Both itraconazole and terbinafine are U.S. Food and Drug Administration (FDA)-labeled for onychomycosis. The mechanism of action of these agents has not been fully determined. Terbinafine is considered fungicidal, and itraconazole is considered fungistatic. They inhibit the production of ergosterol, a vital component of fungal cell-wall synthesis, although the mechanism by which they do so differs between the classes. According to the American Academy of Dermatology guidelines (1996) for the diagnosis and treatment of onychomycosis, the agents appropriate for dermatophyte onychomycosis include fluconazole, griseofulvin, itraconazole, ketoconazole and terbinafine. Both griseofulvin and ketoconazole have fallen out of favor due to a lack of efficacy, significant drug interactions, and side effects. Terbinafine is the only "cidal" antifungal and has the best efficacy profile.

Itraconazole has the longest half-life and can be administered as pulse dosing, characterized by one week of daily dosing followed by three weeks of no drug. Terbinafine is given daily for 6–12 weeks. Terbinafine and itraconazole are extensively bound to plasma proteins. Due to terbinafine's lipophilicity, the terminal half-life of terbinafine from skin and adipose tissue is 200–400 hours. Terbinafine and itraconazole are retained in the nail tissue for up to ten months and six to nine months, respectively, after ingestions. Terbinafine concentrations found in the nail are around 100-fold higher than the minimum inhibitory concentration (MIC) of the drug against dermatophytes.

Several studies published in the literature compared itraconazole to terbinafine. These studies are discussed according to type of onychomycosis, compared agents and type of regimen (continuous or intermittent therapy). Continuous therapy is a drug regimen that is scheduled as regular daily doses given throughout the course of therapy. Intermittent, or pulse therapy, is a drug regimen that is characterized by periods of regular dosing followed by drug-free intervals, or a drug regimen that is dosed once-weekly.

### Dermatophyte Onychomycosis: Terbinafine vs. Itraconazole

- **Continuous Therapy**

Five published studies compare continuous regimens of terbinafine to itraconazole in dermatophyte infections. Follow-up times in these studies ranged from six months to three years following discontinuation of treatment. All these studies used doses and treatment duration recommended by the manufacturer: itraconazole 200 mg daily for 12 weeks or terbinafine 250 mg daily for 12 weeks. Diagnosis was confirmed by potassium hydroxide (KOH) microscopy and culture. Four of the studies were double-blind, randomized, placebo-controlled trials. In each study, both active treatments were significantly better than placebo. However, there was no consensus as to whether itraconazole or

terbinafine was a superior antifungal agent. The Arenas and the Degreef studies did not find significant differences between the two treatment arms. However, the Brautigam (1998), the DeBacker (1998), and the DeCuyper (1999) studies found significant differences in several primary outcomes, especially mycological cure rate. Brautigam and DeBacker both conducted studies which were sponsored by the manufacturer of terbinafine, and both found it was significantly superior to itraconazole in mycological cure rate: Brautigam at one year, and DeBacker at nine months. They also found that terbinafine was superior to itraconazole in percent with a negative culture at the same time-points. DeBacker et al. found significant results in percent with negative microscopy at the nine-month follow-up.

The differences in findings between these studies were not attributable to study size. Degreef et al. (1999), who found no difference, conducted a large study of 292 patients. However, they only followed patients up to six months after treatment was discontinued. The studies that found a significant difference followed patients for nine months or more. When observation is discontinued early, relapses may be missed, and benefits may be underestimated if the agents provide long-term benefits. Terbinafine is a fungicidal agent and, consequently, patients are likely to continue to have improvement long after concentrations in the nail fall below therapeutic levels. DeCuyper et al., who found itraconazole to be superior at nine months, reported that itraconazole-treated patients were more likely to relapse at two years following treatment; however, they did not report statistical values for this finding.

- **Intermittent Therapy**

Three studies compared continuous terbinafine to various pulse regimens, and one study compared a course of pulse terbinafine to pulse terbinafine followed sequentially by itraconazole. Outcomes were assessed at weeks 16, 48, and 72.

Evans et al. (1999) was the only randomized, double-blind, placebo-controlled trial among these studies. It compared continuous terbinafine for 12 and 16 weeks to pulse itraconazole for the same time periods. The authors reported that both arms of terbinafine treatment were superior to itraconazole for all endpoints at week 72 (one year after treatment was discontinued), and that rates of clinical cure for terbinafine improved clearly and consistently until that point. No significant improvement was found with itraconazole beyond week 48.

Tosti et al. (2000) performed two open-label studies. The first compared regimens of pulse terbinafine, pulse itraconazole, and continuous terbinafine, and only followed patients up to six months after discontinuation of treatment. They found that 94% of continuous terbinafine patients and 80% of pulse terbinafine patients achieved mycological cure, compared to only 75% of pulse itraconazole patients. The authors did not report statistical data for this finding, although they did report statistically significant results for other endpoints. The second Tosti study was a follow-up to the first, in which patients who achieved mycological cure were monitored for relapse rate. A higher percentage of patients treated with itraconazole relapsed, but there was no statistical significance. This was a small study, however, and power was not sufficient to detect a difference.

Gupta et al. (2001) compared pulse terbinafine to a combination of pulse terbinafine and itraconazole. This study found statistically significant differences in mycological cure rate at week 72; combination itraconazole/terbinafine was superior to terbinafine alone.

Overall data show that a continuous-dose regimen of terbinafine is superior to pulse-dose itraconazole in the treatment of patients with onychomycosis. Continuous-dose terbinafine may appear to be more effective than pulse-dose terbinafine. Intermittent dosing with either drug may be similar in efficacy.

In 1996, the American Academy of Dermatology published guidelines for the diagnosis and treatment of onychomycosis. Diagnosis is usually the result of careful history and physical examination. However, the guidelines recommend that if systemic therapy is to be used, clinical diagnosis should be confirmed by laboratory tests, such as a potassium hydroxide (KOH) test, or fungal culture. Onychomycosis causes the nails to become thickened, hard to cut and often painful, is worsened by moisture, warmth, trauma, communal bathing and other activities that lead to the exposure of fungi. Common complaints of the disorder are pain, deformed nails and interference with daily activities such as walking, typing, or playing a musical instrument.

Those who suffer from the disease cite a substantial negative effect on their quality of life. Onychomycosis can give rise to complications such as cellulitis and, therefore, further compromise the limb in those with diabetes or peripheral vascular disease. While these complications may not be common, they are certainly serious. Onychomycosis can lead to much more serious consequences in patients with diabetes mellitus, such as nail removal, secondary bacterial infection, and increased risk of amputation. Fungal infection of the nails is also important in immunocompromised patients (i.e., patients diagnosed with human immunodeficiency virus (HIV), positive/acquired immunodeficiency syndrome [AIDS], cancer patients, particularly those taking anticancer medications, and transplant patients who are also taking drugs which suppress the immune system). These patients should be treated immediately to prevent future health problems.

Recommended systemic therapies are summarized in Table 1. Topical therapy is ineffective, and does not resolve distal subungual onychomycosis. Systemic therapy may require as long as six months for fingernails and 12–18 months for toenails. In extreme cases, depending on the degree of patient pain, surgical removal of the nail may be an option.

Table 1: Guidelines for systemic therapy of onychomycosis (American Academy of Dermatology)

Type of Onychomycosis	Infecting Organism	Recommended Therapies
Distal subungual onychomycosis	Dermatophytes	<ul style="list-style-type: none"> <li>• Fluconazole</li> <li>• Griseofulvin*</li> <li>• Itraconazole</li> <li>• Ketoconazole*</li> <li>• Terbinafine</li> </ul>
	Candida albicans	<ul style="list-style-type: none"> <li>• Fluconazole</li> <li>• Itraconazole</li> <li>• Ketoconazole</li> </ul>
	Non-dermatophytes	<ul style="list-style-type: none"> <li>• Itraconazole against some Aspergillus species only</li> </ul>
Superficial white onychomycosis	Any	Topical antifungals

\*Griseofulvin and ketoconazole require continuous therapy until the infected nail has grown out.

In addition, guidelines from the Infectious Diseases Society of America (IDSA) for treatment of candidal onychomycosis have been published. The IDSA recommends that for onychomycosis in general, griseofulvin should not be used, and that newer antifungals, including terbinafine and itraconazole, offer a more effective alternative. With respect to Candida onychomycosis, the IDSA states that terbinafine has very limited activity and that therapy with itraconazole appears to be effective.

Itraconazole and terbinafine have the potential to cause serious hepatotoxicity. Fatalities have occurred with both agents, and there has been no relationship found between total daily dose, duration of therapy or age. Patients should be counseled to report any symptoms of liver dysfunction to their physician. Headache and gastrointestinal disturbances are the most commonly reported adverse reactions. Itraconazole has a black box warning against using it in patients with ventricular dysfunction or congestive heart failure.

Itraconazole is a potent inhibitor of cytochrome 3A4 and has some significant drug interactions. Terbinafine is metabolized by CYP 2D6 and interacts with warfarin, cyclosporine, theophylline and tricyclic antidepressants.

Terbinafine dosage recommendations for toenail onychomycosis is 250 mg per day for 12 weeks. For fingernails, the dose is 250 mg per day for six weeks. Liver enzyme levels and a complete blood count should be obtained before initiation and every four to six weeks thereafter. Terbinafine should be stopped if the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels become elevated twice above normal.

Itraconazole dosage recommendations for the treatment of toenail onychomycosis is 200 mg once daily for 12 weeks. For fingernails, the dose is 200 mg twice a day for one week and then repeated again after a three-week washout period. Itraconazole has also successfully been used to treat toenail onychomycosis with pulse dosing.

Itraconazole should be taken with food. Liver enzymes should be measured before initiating continuous treatment and then every four to six weeks. There is no monitoring recommendation for pulse treatment.

**Note:** CIGNA allows PULSE DOSING with itraconazole (Sporanox®) ONLY. There is a maximum of TWO pulses for fingernails and THREE pulses for toenails.

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## Coding/Billing Information

**Note:** This section is not in use.

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