Ciclopirox

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 13. Dermatological medicines > 13.1. Dermatological medicines > Antifungal medicines

ATC codes: D01AE14

Indication	Onychomycosis ICD11 code: EE12.1
INN	Ciclopirox
Medicine type	Chemical agent
List type	Core
Formulations	**Local > Topical > Solution:** 80 mg per g (as hydroxypropyl chitosan)
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Ciclopirox
DrugBank	Ciclopirox

Expert Committee recommendation

The Expert Committee acknowledged that onychomycosis, despite its non-life-threatening nature, can cause localized pain and social embarrassment, and negatively affect quality of life. It is often difficult to treat, with treatment duration being lengthy and associated with high rates of failure, poor adherence and increased risk of relapse. In consideration of the evidence presented in the application, the Committee noted that while topical application of ciclopirox 8% hydroxypropyl chitosan demonstrated broad-spectrum antifungal activity, complete cure rates remained low (about 15% or less). The Committee noted that ciclopirox has limited efficacy in severe cases of onychomycosis, especially when the nail matrix is involved. The safety profile was generally favourable, with mild and localized adverse events such as nail discolouration. However, no evidence from head-to-head trials with oral or combined oral and topical antifungal treatments were presented, nor were any comparative cost–effectiveness studies. Therefore, the Expert Committee did not recommend the inclusion of ciclopirox hydroxypropyl chitosan nail hydrolacquer on the EML for the treatment of onychomycosis in adults because of the lack of robust evidence of comparative benefits and safety versus oral or combined oral and topical antifungal treatments, and unknown comparative cost–effectiveness.

Background

Ciclopirox has not been previously evaluated for inclusion on the EML. The EML currently includes systemic and

topical antifungals for other indications.

Public health relevance

Onychomycosis is a broad descriptor for fungal infections of the nail that are caused by dermatophytes, yeasts and saprophytic moulds. Onychomycosis caused by dermatophytes are responsible for about 60–70% of all infections, while yeasts account for about 20% (1). Onychomycosis is a progressive but not life-threatening disease. The global prevalence of onychomycosis has been reported at around 10% (2), but it may be as high as 48% in some settings (3). Prevalence increases with age, reaching over 50% in adults 70 years or older (4). Onychomycosis often presents with nail discolouration, separation, brittleness or thickening that typically worsens with time. These clinical signs may cause localized pain and social embarrassment and contribute to negative quality of life (5). Onychomycosis is often difficult to treat and is associated with high rates of treatment failure and recurrence. Systemic treatment with oral antifungals requires prolonged treatment and is also associated with relatively low cure rates (1).

Benefits

Ciclopirox has antimicotic activity against dermatophytes, yeasts and non-dermatophyte moulds. It may be fungistatic or fungicidal depending on concentration and duration of contact with target organisms. It also has antibacterial activity against gram-positive, gram-negative aerobic and anaerobic bacteria (6). HPCH is a formulation technology to increase the permeation of ciclopirox into the nails (7). Systematic reviews and meta-analyses A 2020 Cochrane systematic review of 56 randomized controlled trials (12 501 participants) assessed the clinical and mycological effects of topical and device-based therapies for toenail onychomycosis in adults (8). Most studies were between 48 and 52 weeks in duration and were conducted in the outpatient setting. The review included studies of both ciclopirox 8% HPCH hydrolacquer and ciclopirox water insoluble lacquer. The primary efficacy outcome of the review was complete cure rate, defined as the proportion of participants with 0% nail plate involvement and mycological cure at follow-up. For the comparison of ciclopirox 8% HPCH hydrolacquer versus active comparators (ciclopirox 8% water insoluble lacquer or amorolfine 5% lacquer; two randomized controlled trials, 490 participants), the review found moderate-quality evidence that ciclopirox 8% HPCH hydrolacquer would probably lead to complete cure compared with the comparators (12.8% versus 5.2%, risk ratio (RR) 2.43, 95% confidence interval (CI) 1.32 to 4.48). For the comparison of ciclopirox 8% water insoluble lacquer versus vehicle (two randomized controlled trials, 460 participants), the review found low-quality evidence that ciclopirox may lead to complete cure compared with vehicle (6.9% versus 0.4%, RR 9.29, 95% CI 1.72 to 50.14). A 2015 network meta-analysis of 19 randomized controlled trials (5551 participants) evaluated the relative efficacy of different treatments for onychomycosis (9). The trials had a parallel-group design and a study duration of at least 48 weeks. The treatments analysed included: oral itraconazole, fluconazole and terbinafine; topical ciclopirox 8% water-insoluble and amorolfine lacquers; and topical terbinafine, tavaborole and efinaconazole nail solutions. All treatments were significantly superior to placebo for mycological cure, the most effective being oral terbinafine 250 mg (odds ratio (OR) 46.72, 95% CI 24.38 to 101.34) and pulse itraconazole 400 mg (OR 18.36, 95% CI 6.14 to 63.33). The OR for ciclopirox 8% water-insoluble lacquer was 4.25 (95% CI 2.25 to 8.12). No significant differences were seen between ciclopirox 8% water-insoluble lacquer and other topical treatments for mycological cure; however, point estimates favoured ciclopirox in comparisons with amorolfine lacquer (OR 1.09, 95% CI 0.31 to 3.61) and terbinafine nail solution (OR 1.04, 95% CI 0.36 to 2.92). All oral treatment were significantly superior to topical treatments. Randomized trials A 2009 company-sponsored multicentre, randomized, three-arm, trial evaluated the efficacy and safety of ciclopirox 8% HPCH hydrolacquer versus ciclopirox 8% water insoluble lacquer and placebo in 467 patients with onychomycosis (24–100% nail involvement) (10). Patients were randomized 2:2:1 to receive 48 weeks of treatment (daily application), followed by a 12-week follow-up period. The primary endpoint was complete cure, defined as conversion to negative of both potassium hydroxide microscopy and fungal culture, and 100% growth of healthy nail at week 48 and week 52. The complete cure rate was 5.7%, 3.2% and 0% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. During the treatment period, ciclopirox 8% HPCH was found to be superior to placebo and non-inferior to ciclopirox 8% water insoluble lacquer. At the end of the follow-up period, ciclopirox 8%

HPCH was clinically and statistically superior to ciclopirox 8% water insoluble lacquer (12.7% versus 5.8%; P < 0.05). Response rates at 48 weeks were 24%, 17.3% and 6.4% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. A post hoc analysis of the above-mentioned trial, evaluated the efficacy of ciclopirox 8% HPCH in the subset of 302 patients with mild to moderate onychomycosis (≤ 50% nail involvement) (11). Complete cure rates after 48 weeks were 7.6%, 3.3% and 0% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. After 60 weeks, the corresponding complete cure rates were 15.1%, 5.8% and 1.6%. Response rates at 48 weeks were 31.9%, 24.2% and 9.5% for the ciclopirox 8% HPCH hydrolacquer, ciclopirox 8% water insoluble lacquer and placebo groups, respectively. Ciclopirox 8% HPCH was significantly superior to placebo at week 48 (P = 0.001), however the difference at week 60 was not significant (P = 0.052). A 2015 company-sponsored randomized, controlled, parallel-group clinical trial compared the effectiveness and safety of ciclopirox 8% HPCH hydrolacquer and amorolfine 5% lacquer in 120 patients with mild to moderate toenail onychomycosis (12). Patients were randomized 1:1 to receive daily application of ciclopirox 8% HPCH hydrolacquer or twice weekly application of amorolfine 5% lacquer. Primary efficacy outcomes were complete cure rate, treatment success, and mycological cure, evaluated at different times up to 48 weeks in the intention-to-treat population. Ciclopirox 8% HPCH was significantly superior to amorolfine 5% for complete cure rate at week 48 (35.0% versus 11.7%; P < 0.001). The difference in cure rate between treatments was not significant at week 24. At week 48, ciclopirox 8% HPCH was also significantly superior to amorolfine 5% for the outcomes of treatment success (58.3% versus 26.7%; P < 0.001) and mycological cure (100% versus 81.7%; P < 0.001). Numbers-needed to treat for complete cure were computed as 3 and 11 for ciclopirox and amorolfine, respectively. A 2015 non-interventional study in Germany evaluated the effectiveness of ciclopirox HPCH hydrolacquer in 70 patients on whom prior treatment with amorolfine lacquer had failed (13). The primary outcome was the conversion to negative mycological findings (potassium hydroxide test and culture) at 24 weeks. For the primary outcome, response rates for treatment success and treatment failure with ciclopirox 8% HPCH in the full analysis set were 58.6% and 41.4%, respectively.

Harms

In the 2020 Cochrane systematic review there was low-quality evidence of an increased risk of adverse events associated with ciclopirox 8% water-insoluble lacquer than vehicle (11.3% versus 7%, RR 1.61, 95% CI 0.89 to 2.92; two randomized controlled trials, 460 participants). The most commonly reported adverse events were application-site reactions (transient tingling, burning, or pain with treatment use), rashes (mild erythema in the skin surrounding the nail) and alterations in nail colour or shape. The risk of adverse events was similar between for ciclopirox 8% HPCH hydrolacquer and active comparators (ciclopirox 8% water-insoluble lacquer and amorolfine 5%: 6.3% versus 12.1%; RR 0.60, 95% CI 0.19 to 1.92; two randomized controlled trials, 487 participants, low quality of evidence) (8). From the 2009 trial of ciclopirox 8% HPCH hydrolacquer versus ciclopirox 8% water insoluble lacquer and placebo, no serious or severe adverse events were reported in any treatment arm. Local application-site signs and symptoms such as itching, burning, pain, erythema or oedema were all mild-to-moderate and less frequent with ciclopirox 8% HPCH than with ciclopirox 8% water insoluble lacquer (10).

Additional evidence

A 2020 systematic review and network meta-analysis evaluated the effectiveness and safety of monotherapy and combination treatments for toenail onychomycosis (14). Of 75 records meeting the inclusion criteria for the quantitative analysis, only 26 (8136 participants, 31 trials) met the criteria for network meta-analysis reporting mycological cure rates or adverse events. Treatments in the evidence network were ciclopirox 8% water insoluble lacquer, efinaconazole 10% topical solution, oral fluconazole, oral itraconazole, oral terbinafine and tavaborole 5% solution. Amorolfine, ciclopirox 8% HPCH hydrolacquer, griseofulvin, devised-based therapies and combination therapies were unable to be included in the network. All treatments were significantly superior to placebo for mycological cure, the most effective being continuous itraconazole 200 mg (OR 18.61, 95% CI 7.40 to 46.81) and continuous terbinafine 250 mg (OR 16.41, 95% CI 6.49 to 41.47). The OR for ciclopirox 8% water insoluble lacquer was 4.11 (95% CI 2.21 to 7.64). Ciclopirox 8% water insoluble lacquer was not significantly different from other topical treatments, pulse terbinafine 500 mg, pulse itraconazole 400 mg or fluconazole for mycological cure.

Topical treatments had the lowest surface under the cumulative ranking curve (SUCRA) scores of all treatments evaluated. With the exception of efinaconazole 10%, for which more transient application-site reactions were reported, the risk of adverse events with any of the treatments were not significantly different from placebo.

Cost / cost effectiveness

No studies evaluating the cost or cost-effectiveness of ciclopirox 8% HPCH hydrolacquer were identified in the literature search conducted for the purpose of the application. The application reported publicly available prices for ciclopirox 8% HPCH in 20 of the 39 markets in which it is available. Prices ranged from 9.44 United States dollars (US$) (France) to US$ 35.40 (Switzerland) for 3.3 mL and from US$ 16.42 (France) to US$ 47.40 (Finland) for 6.6 mL.

WHO guidelines

WHO guidelines for the treatment of onychomycosis are not currently available. The 2024 edition of the Pan American Health Organization's guide for the treatment of infectious diseases (15) includes the following oral treatment recommendations for onychomycosis in adults: Fingernails • First choice: terbinafine 250 mg a day or 500 mg a day for 1 week every month, for 6–8 weeks; • Other options: itraconazole 200 mg a day for 3 months or 200 mg twice daily for 1 week every month for 2 months; fluconazole 300–450 mg once weekly for 3−6 months. Toenails • First choice: terbinafine 250 mg a day for 3–4 months; • Other options: itraconazole 200 mg a day for 3 months or 200 mg twice daily for 1 week every month for 3–4 months; fluconazole 300–450 mg once weekly for 6−12 months. The application reported that topical ciclopirox (both HPCH hydrolacquer and water insoluble lacquer) is recommended by numerous international and national guidelines and other scientific articles.

Availability

The application reported that ciclopirox 8% HPCH has regulatory approval and market availability in 39 countries globally. Ciclopirox 8% water-insoluble lacquer has regulatory approval and market availability in 33 countries globally. In many of these countries, it is available as an over-the-counter product.

Other considerations

Resistance to oral antifungals is increasing, with resistant yeast and mould species associated with systemic infections categorized by WHO as fungal pathogens posing a significant threat to public health (16). Resistant strains prolong disease duration, increasing the opportunity for disease transmission, thereby increasing infection rates and encouraging disease spread (17). A 2024 review discussed the role of antifungal stewardship and topical antifungals in the treatment of onychomycosis (17). The review noted that no natural dermatophyte resistance to topical antifungals has been reported, suggesting no liability to induce dermatophyte resistance as validated by in vitro studies. Ciclopirox has also been noted for its effectiveness against terbinafine- and azole-resistant fungal species. It was also noted that combination topical and oral antifungal treatment may reduce treatment failure caused by primary resistance and limit the development of a secondary resistance while also improving treatment adherence. In contrast to other topical antifungals for onychomycosis that target the ergosterol synthesis pathway, ciclopirox has a unique mechanism of action against which the pathogen is unable to adapt by mutating the binding site of the targeted enzyme. Specifically, it is distinguished from therapeutic alternatives due to its chelation of polyvalent metal cations, leading to the inhibition of many cellular activities and modifications to the fungal plasma membrane. This mechanism is indicative of a lower propensity for inducing antifungal resistance in the species that contribute to onychomycosis. An important factor in preventing the development of resistance is the ability of medicines with fungicidal activities to permeate the nail and reach the site of infection. In this regard, in vitro studies have shown that the permeability of ciclopirox 8% HPCH hydrolacquer is about 10 times greater than that of efinaconazole and significantly improved relative to ciclopirox water insoluble lacquer (18). It has been hypothesized that these results were also attributable to the ability of ciclopirox to accumulate in the nail, enabling gradual release into both the nail plate and nail bed. Similarly, in contrast to terbinafine, itraconazole and amorolfine, where resistant strains were identified in vitro, no mutant resistance to ciclopirox was

identified in Trichophyton rubrum strains (19). The Control and Response Strategies unit within the Antimicrobial Resistance Division reviewed and provided comments on the application. The technical unit did not support the inclusion of ciclopirox HPCH on the EML due to insufficient evidence. The technical unit also noted the need for a more comprehensive review of all available topical and systemic treatments for onychomycosis. However, in the context of competing priorities, the unit did not consider that such a review was a high priority at this time.

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