Proposal for the Inclusion of Ciclopirox Hydroxypropyl Chitosan in the WHO Model List of Essential Medicines for the Treatment of Onychomycosis in Adult Patients

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Table of Contents

List of Tables

List of Supplementary Tables

List of Figures

List of Supplementary Figures

Acronyms

AAFP	American Academy of Family Physicians
AEMPS	Spanish Agency of Medicines and Medical Devices
AGEMED	State Agency for Medicines and Health Technologies (Bolivia)
AIFA	Italian Medicines Agency
AMO	Amorolfine
ANAMED	National Medicines Agency in Chile
ANMAT	National Administration of Medicines, Food and Medical Technology (Argentina)
ANSM	French National Agency for Medicines and Health Products Safety
ARCSA	National Agency for Regulation, Control, and Health Surveillance (Ecuador)
ATC	Anatomical Therapeutic Chemical
AWMF	Association of the Scientific Medical Societies of Germany
BAD	British Association of Dermatologists
BASG	Austrian Federal Office for Safety in Health Care
BDA	Bulgarian Drug Agency
BfArM	German Federal Institute for Drugs and Medical Devices
CE	Cost-Effectiveness
CI	Confidence Interval
COFEPRIS	Federal Commission for the Protection against Sanitary Risk (Mexico)
DFD	Disease-Free Day
DIGEMID	General Directorate of Medicines, Supplies, and Drugs (Peru)
DKMA	Danish Medicines Agency
DLSO	Distal and Lateral Subungual Onychomycosis
EML	Essential Medicines List
EMLc	Essential Medicines List for children
EOF	National Organization for Medicines (Greece)
EU	Efficacy Unit
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
FAS	Full Analysis Set
FIMEA	Finnish Medicines Agency
FOPH	Federal Office of Public Health (Switzerland)
GBD	Global Burden of Disease
HPCH	Hydroxypropyl Chitosan

HPRA	Health Products Regulatory Authority (Ireland)
ICER	Incremental Cost-Effectiveness Ratio
IMSEAR	Index Medicus for South-East Asia Region
INFARMED	Portuguese National Authority of Medicines and Health Products
INHRR	National Institute of Hygiene “Rafael Rangel” (Venezuela)
INN	International Non-proprietary Name
INVIMA	National Institute for Food and Drug Surveillance (Colombia)
ISPCH	Public Health Institute of Chile
ITT	Intention-to-treat
JAZMP	Agency for Medicinal Products and Medical Devices (Slovenia)
KOH	Potassium Hydroxide
LV	Swedish Medical Products Agency
MEDSAFE	New Zealand Medicines and Medical Devices Safety Authority
MFDS	Ministry of Food and Drug Safety (South Korea)
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
mITT	Modified intention-to-treat
MNF	Manufacturer
MOPH	Ministry of Public Health (Lebanon)
NA	Not Available
NAMMDR	National Agency for Medicines and Medical Devices (Romania)
NCSS	Number Cruncher Statistical System
NDM	Non-Dermatophyte Mould
NIS	Noninterventional Study
NMA	Network Meta-Analysis
NOMA	Norwegian Medical Products Agency
NSI	Nail Society of India
OGYÉI	National Institute of Pharmacy and Nutrition (Hungary)
OR	Odds Ratio
PAHO	Pan American Health Organization
PGE2	Prostaglandin E2
PP	Per Protocol
PPP	Pharmacy Purchase Price
PPI VAT	Public Price Including Value-Added Tax
PHS	Pharmaceutical Services (Cyprus)
Roszdravnadzor	Federal Service for Surveillance in Healthcare (Russia)

SemFYC	Spanish Society of Family and Community Medicine
SEMG	Spanish Society of General and Family Physicians
SEF	Symptom-Free Day
SEQ	Sequential
SLR	Systematic Literature Review
SÚKL	State Institute for Drug Control (Czech Republic)
ŠÚKL	State Institute for Drug Control (Slovakia)
SWO	Superficial White Onychomycosis
TGA	Therapeutic Goods Administration (Australia)
URPL	Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products (Poland)
VVKT	State Medicines Control Agency (Lithuania)
WHO	World Health Organization
ZVA	State Agency of Medicines (Latvia)

1. Summary Statement of the Proposal for Inclusion

This application is for the inclusion of Ciclopirox 8% hydroxypropyl chitosan (HPCH) medicated nail hydrolacquer as an individual medicine in the core list of the Essential Medicines List (EML) for the treatment of onychomycosis in adult patients.

Onychomycosis is a common nail infection associated with significant physical and psychological morbidity. Although not life threatening, fungal nail infections are an important public health concern due to their high prevalence, poor response to therapy and significant clinical, social, and financial impact. Onychomycosis is more difficult to treat than most dermatophytosis (e.g., skin dermatophytosis) due to the inherent slow growth of the nail and the deep-seated nature of the fungus within the nail plate. Ciclopirox is a broad-spectrum antifungal agent with activity against dermatophytes, yeasts, and moulds, including certain frequently azole-resistant species.

Ciclopirox is available as an 8% HPCH hydrolacquer and evidence supports the use for the treatment of onychomycosis caused by dermatophytes, yeasts and other moulds (Ciclopirox-sensitive fungi). HPCH is a film-forming polymer that increases ciclopirox nail permeation, nail hardness and resistance to rupture; it can reinforce the nail structure and prevent the establishment of new or recurring fungal infections with repeated applications.

2. Consultation with WHO Technical Departments

Not Applicable.

3. Other Organization(s) Consulted and/or Supporting the Submission

Not applicable.

4. Key Information summary table for Ciclopirox

4.1. International Non-proprietary Name of the Medicine

International Non-proprietary Name (INN)

Ciclopirox

4.2. Anatomical Therapeutic Chemical Code of the Medicine

Anatomical Therapeutic Chemical (ATC)

In the ATC classification system, ciclopirox is classified as “other antifungals for topical use” and can be identified by the ATC code: D01AE14. *(1)*

4.3. Dosage Form(s) and Strength(s) Proposed for Inclusion

Ciclopirox is available as an 8% hydrolacquer with hydroxypropyl chitosan (HPCH), a film-forming polymer, as an excipient. Table 1 shows the presentations and formulations currently available.

Table 1. Currently available presentations and formulations of Ciclopirox 8% HPCH hydrolacquer for treatment of onychomycosis

Pharmaceutical form	Route of administration	Formulation	Strength	Packaging	Package size
Medicated nail Lacquer	Topical	Hydrolacquer	80 mg/g	Bottle	6.6 mL
Medicated nail Lacquer	Topical	Hydrolacquer	80 mg/g	Bottle	3.3 mL

Note: The table above is based on the available formulations of the originator (Ciclopirox medicated nail hydrolacquer with hydroxypropyl chitosan [HPCH] as excipient). | Acronyms: HPCH: Hydroxypropyl Chitosan.

4.4. Indication(s)

Ciclopirox 8% HPCH hydrolacquer is indicated for the treatment of onychomycosis in adult patients. Table 2 shows the detail on indications authorised according to a selection of regulatory agencies worldwide.

Table 2. Ciclopirox 8% HPCH indications from a selection of regulatory agencies

Country	Regulatory agency	Ciclopirox 8% HPCH hydrolacquer indication
Argentina	National Administration of Medicines, Food and Medical Technology - Argentina (ANMAT)	Topical treatment of mild to moderate onychomycosis of nails (without matrix involvement) caused by *Trichophyton rubrum*. *(2)*
Australia	Therapeutic Goods Administration (TGA)	Topical treatment of mild to moderate onychomycosis, without lunular involvement, due to dermatophytes, yeasts and moulds. *(3)*
Austria	Austrian Federal Office for Safety in Health Care (BASG)	Mild to moderately severe fungal infections of the nails caused by dermatophytes and/or other ciclopirox-sensitive moulds, without involvement of the nail matrix. *(4)*

Country	Regulatory agency	Ciclopirox 8% HPCH hydrolacquer indication
Belgium	Federal Agency for Medicines and Health Products (FAMHP)	Mild to moderate fungal infections of the nails caused by dermatophytes, yeasts and fungi, without involvement of the nail matrix/lunula. *(5)*
Bolivia	State Agency for Medicines and Health Technologies (AGEMED)	Treatment of mild to moderate fungal nail infections (onychomycosis) caused by wailing fungi and/or other fungi that could be cured with ciclopirox. *(6, 7)*
Bulgaria	Bulgarian Drug Agency (BDA)	Mild to moderate nail fungal infection. *(8, 9)*
Chile	National Medicines Agency in Chile (ANAMED)	Topical treatment of mild to moderate onychomycosis (without matrix involvement) caused by *Trichophyton rubrum*. *(10)*
Colombia	National Institute for Drug and Food Surveillance (INVIMA)	Not available at public domain. *(11)*
Cyprus	Pharmaceutical Services (PHS)	Mild to moderate fungal nail infections caused by dermatophytes, yeasts and *Eurotomycetes*, when there is no involvement of the nail matrix/meniscus. *(12)*
Czech Republic	State Istitute for Drug Control (SÚKL)	Mild to moderate mycotic nail infections caused by dermatophytes and/or other filamentous fungi sensitive to ciclopirox, unless the nail bed is affected. *(13)*
Denmark	Danish Medicines Agency (DKMA)	Mild to moderate nail fungal infections caused by dermatophytes, yeasts and moulds without involvement of the nail bed/lunula for adults. *(14)*
Ecuador	National Agency for Health Regulation, Control and Surveillance	Not available at public domain. *(15)*
Finland	Finnish Medicines Agency (FIMEA)	Mild to moderate nail fungal infections caused by dermatophytes, yeasts and moulds that have not spread to the nail bed or lunula. *(16)*
France	French National Agency for Medicines and Health Products Safety (ANSM)	Mild to moderate onychomycosis caused by dermatophytes and/or other ciclopirox-sensitive moulds, without damage of the nail matrix. *(17)*
Germany	German Federal Institute for Drugs and Medical Devices (BfArM)	Fungal diseases of the nails caused by dermatophytes and/or other ciclopirox-sensitive moulds. *(18)*
Greece	National Organization for Medicines (EOF)	Mild to moderate fungal infections of the nails caused by dermatophytes, and/or other fungi sensitive to ciclopirox, when there is no involvement of the nail matrix. *(19)*

Country	Regulatory agency	Ciclopirox 8% HPCH hydrolacquer indication
Hungary	National Institute of Pharmacy and Nutrition (OGYÉI)	Mild to moderate infections of the nails caused by Dermatophyton and/or other ciclopirox-sensitive fungi without involvement of the nail matrix. *(20)*
Ireland	Health Products Regulatory Authority (HPRA)	Mild to moderate fungal infections of the nails caused by dermatophytes, yeasts and moulds, without nail matrix/lunula involvement. *(21)*
Israel	Israel Ministry of Health - Pharmaceutical Division	Fungal infections of the nails caused by ciclopirox-sensitive fungi. *(22, 23)*
Italy	Italian Medicines Agency (AIFA)	Mild to moderate onychomycosis caused by dermatophytic moulds and/or ciclopirox-sensitive moulds, without involvement of the nail matrix. *(24)*
(South) Korea	Ministry of Food and Drug Safety (MFDS)	Onychomycosis (hand and toenail fungus). *(25)*
Latvia	State Agency of Medicines (ZVA)	Mild to moderate nail fungal infections caused by dermatophytes, yeasts and moulds when the nail matrix/lunula is not involved. *(26)*
Lebanon	Pharmacy Directorate - Ministry of Public Health	Not available at public domain. *(27)*
Lithuania	State Medicines Control Agency (VVKT)	Treatment of mild to moderate fungal infections of the nail caused by dermatomycetes, yeasts or moulds when the nail matrix (lunula) is intact. *(28)*
Mexico	Federal Commission for the Protection against Health Risks (COFEPRIS)	Not available at public domain. *(29)*
New Zealand	New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE)	Mild to moderate fungal nail infections that does not involve the lunula. *(30)*
Norway	Norwegian Medical Products Agency (NOMA)	Mild to moderate fungal nail infections caused by dermatophytes, yeasts and molds, not involving the nail matrix/lunula. *(31)*
Peru	Directorate General of Medicines, Supplies and Drugs	Mild to moderate fungal nail infections in adults, caused by dermatophytes and other fungi sensitive to ciclopirox, without involvement of the nail matrix. *(32)*
Poland	Poland Ministry of Health	Mild to moderate fungal nail infections caused by dermatophytes and/or other ciclopirox-sensitive fungi, when the infection has not taken over the nail matrix. *(33)*

Country	Regulatory agency	Ciclopirox 8% HPCH hydrolacquer indication
Portugal	Portuguese National Authority of Medicines and Health Products (INFARMED)	Mild to moderate fungal infections of the nails, caused by dermatophytes and/or other moulds sensitive to ciclopirox, without involvement of the nail matrix. *(34)*
Romania	National Agency for Medicines and Medical Devices (NAMMDR)	Mild to moderate localized mycotic infections of the nail caused by dermatophytes and/or other ciclopirox-sensitive fungi, without damage to the nail matrix. *(35)*
Russia	Federal Service for Surveillance in Healthcare (Roszdravnadzor)	Treatment and prevention of fungal infections of the skin and mucous membranes (including onychomycosis). *(36)*
Slovakia	State Institute for Drug Control (ŠÚKL)	Mild to moderate mycotic nail infections caused by dermatophytes and/or other fungi sensitive to ciclopirox, without nail bed involvement. *(37)*
Slovenia	Agency for Medicinal Products and Medical Devices (JAZMP)	Mild to moderate fungal nail infections caused by dermatophytes, yeasts and moulds when the nail matrix/lunula is unaffected. *(38)*
Spain	Spanish Agency of Medicines and Medical Devices (AEMPS)	Mild to moderate fungal nail infections caused by dermatophytes and other moulds sensitive to ciclopirox, without involvement of the nail matrix. *(39)*
Sweden	Swedish Medical Products Agency (LV)	Mild to moderately severe nail fungal infections caused by dermatophytes, yeasts or molds, not involving the nail matrix/lunula. *(40)*
Switzerland	Federal Office of Public Health (FOPH)	Mild to moderate fungal infections of the nails caused by dermatophytes and/or other ciclopirox-sensitive fungi in which the nail matrix is not affected. *(41)*
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)	Mild to moderate fungal infections of the nails caused by dermatophytes, yeasts and moulds, without nail matrix/lunula involvement. *(42)*
Venezuela	National Institute of Hygiene “Rafael Rangel” (INHRR)	Coadjuvant in the treatment of superficial mycosis of the nails. *(43)*

5. Proposal for an Individual Medicine or Representative of a Pharmacological Class / Therapeutic Group

This application is for the inclusion of ciclopirox 8% HPCH medicated nail hydrolacquer as an individual medicine in the core list of the EML in subsection 13.1 (Dermatological medicines / Antifungal medicines) for the treatment of onychomycosis in adult patients.

6. Information Supporting the Public Health Relevance

6.1. Disease Overview

Nearly a billion people are estimated to have skin, nail and hair fungal infections, *(44)* making them the most common type of human infection worldwide. *(45)* Accordingly, dermatological diseases are a significant and understated burden within global health. In fact, Global Burden of Disease (GBD) studies have recognized that they collectively represent the world's fourth leading cause of non-fatal burden. *(46, 47)* Skin diseases afflict people across all demographic groups and in all countries irrespective of the income levels. Differential access to health care influences early detection, diagnosis, and outcome of treatment. Amongst skin conditions, the 2019 GBD Study revealed that since 1990, fungal skin diseases are the major contributors to the incidence of skin and subcutaneous diseases worldwide, especially in South-Asia. Particularly concerning was their ever-growing incidence both within and outside of their endemic areas, because of the increasing number of immunocompromised patients and prominence of global travel. *(48)*

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 ~20% of infections. *(49)* Notably, in warmer climates, non-dermatophyte, yeast and mixed infections are more common than previously thought. For instance, in warm and humid countries in Africa, 84% of onychomycosis-related infections are caused by yeasts, mostly by *Candida spp. (50)*

Onychomycosis accounts for half of all nail disease cases. *(49)* Global prevalence of onychomycosis is ~10% and can go up to 48% in countries like Mexico. *(51)* The prevalence of onychomycosis increases with age, as one retrospective study found that prevalence was ≥ 20% in adults 60 years or older and ≥ 50% in adults 70 years or older. *(52)* Other significant risk factors for the disease include repeated nail trauma and a history of *Tinea pedis*. Several co-morbidities, including diabetes, obesity, immunosuppression, and other malignancies are also associated with an elevated risk of developing onychomycosis. *(53)* In part due to the growing prevalence of some of its associated risk factors around the world, most notably advanced age and diabetes, incidence of onychomycosis is rising. *(52)*

Onychomycosis often presents with nail discolouration, separation, brittleness or thickening that typically worsens with time. *(54)* However, onychomycosis is more than just a cosmetic problem. It is a progressive disease that, while not life-threatening, requires specific and appropriate treatment. These clinical signs may cause localized pain which, alongside social embarrassment, may contribute to negative quality of life. Social embarrassment and an underestimation of the medical importance of the condition often leads to patients not bringing the infection to the attention of their healthcare practitioner. *(54)*

Unfortunately, onychomycosis is difficult to treat, as indicated by high rates of treatment failure and recurrence (up to 53%). *(49)* One reason might be antifungal resistance and the formation of dormant fungal cells by the pathogen, known as spores, which can survive in the affected nail keratin, thereby evading the effect of antifungal drugs. *(55, 56)* In most cases, patients receive oral antifungals*, (49)* which require prolonged treatment and can be accompanied by a myriad of adverse events (AEs), such as hepatotoxicity. *(57-59)* Even these oral treatments have relatively low complete cure rates of 35%-55%, 14%-43%, and 21%-48% for terbinafine, itraconazole and fluconazole, respectively. *(49)* Complete cure rate can be defined as negative KOH + Negative culture + nail totally cleared, a composite efficacy variable that can be difficult to achieve. Other efficacy variables include modified cure rate (negative culture + Nail totally cleared [no need for KOH assay. KOH assay allows the visualization of hyphae, that might not be viable and therefore can interfere with the interpretation of cure]); response rate (negative KOH + Negative culture + <10% residual nail involvement [considering that <10% involvement is a therapy success]); modified response rate (Negative culture + <10% residual nail involvement); and mycological cure (Negative KOH + Negative culture). *(60)*

Treatment is further complicated by the widespread neglect of some dermatological conditions in many geographies, which are falsely considered to be addressable with hygienic improvements.

Antifungal resistance is a growing concern, especially in India and parts of Europe, with one study in the former concluding that four commonly used antifungal drugs were similarly ineffective, with cure rates of 8% or less at 4 weeks. *(61)* Over the past two decades, resistance to the first-line oral treatments itraconazole and terbinafine has been steadily increasing among *Trichophyton* species. Azoles and terbinafine exert their antifungal activity through the inhibition of ergosterol biosynthesis. *(62, 63)* South Asia has been particularly afflicted by infections caused by *T. indotineae*, which has several point mutations in the squalene epoxidase Erg1 and the sterol 14-α demethylase Erg11 genes, which encodes for the molecular target of terbinafine and azoles, respectively. *(64) T. indotineae* induced *Tinea corporis*, *Tinea cruris* and *Tinea faciei* have reached epidemic levels in India, largely due to its non-response to terbinafine and cases reported in Europe, Canada and China have been traced to travel from the region. Finally, the deficit of surveillance suggests that the global

scale of antifungal resistance is likely underestimated, which when coupled with the dearth of effective treatment options, indicates a credible risk of a public health crisis. *(64)* It has also been noted that the limited number of available anti-fungal agents classes and few new approvals in recent years means that few fungal adaptations are required to induce resistance to treatment. This recent development further highlights the need for a greater diversification of treatment options, as highlighted by the Global Action Fund for Fungal Infections. *(65)*

6.2. Target Population

Adult patients with a fungal infection of the nail (onychomycosis) caused by dermatophytes, yeasts, or other non-dermatophyte moulds sensitive to ciclopirox.

6.3. Alternative Medicines Currently Included in the Model Lists

There are no medicines currently included in the EMLs indicated specifically for onychomycosis.

However, there are twelve antifungal medicines included in the EMLs. *(66)* Eight are listed within section 6 “Anti-infective Medicines” within subsection 3 “Antifungal medicines” and include:

- Itraconazole and voriconazole both for the treatment of chronic pulmonary fungal infections and other fungal infections
- Amphotericin B in its parental form is meant for the treatment of potentially life-threatening fungal infections
- Clotrimazole is only listed in its vaginal cream and tablet forms
- Fluconazole in its capsule, injection, oral liquid and powder for oral liquid forms
- Flucytosine in its capsule and injection forms
- Griseofluvin in its liquid and solid oral dosage forms
- Nystatin in its oral (liquid and solid) and topical dosage forms

A further four are listed within section 13 “Dermatological Medicines” within subsection 1 “Antifungal medicines” and include:

- Miconazole as a cream or ointment
- Selenium sulfide as a detergent-based suspension
- Sodium thiosulfate as a solution
- Terbinafine as a cream or ointment

7. Treatment Details

7.1. Ciclopirox

Ciclopirox is an **hydroxypyridone derivative** with **antimicotic activity** against a very broad spectrum of microorganism, as it inhibits:

- Dermatophytes
- Yeasts (including certain frequently azole-resistant *Candida* species)
- Non-dermatophyte moulds
- Bacteria (particularly beneficial in the treatment of mixed infections)

The main antifungal mechanism of action for ciclopirox is chelation of trivalent metal cations, especially iron chelation, which causes the inhibition of metal-dependent enzymes that are responsible for the degradation of reactive oxygen species in the fungal cell. As a consequence, ciclopirox targets diverse metabolic (e.g., respiratory) and energy producing processes in microbial cells. This unique mechanism of action differs from that of most antifungals, such us azoles and terbinafine, which act trough ergosterol synthesis inhibition, and provides ciclopirox **a very low potential** for the **development of resistance** in pathogenic fungi. *(67-69)*

Ciclopirox can be either **fungistatic or fungicidal**, depending on the concentration and the duration of contact with target organisms. *(67)* Ciclopirox also has **antibacterial activity** against gram-positive, gram-negative aerobic and anaerobic bacteria, with a broader spectrum of action and a uniform antibacterial efficacy against all strains at concentrations ranging from 32 to 128 µg/mL. *(67-70)* This is specially important because under certain conditions, onychomycosis might be complicated by secondary bacterial infections. *(67)* Ciclopirox is also associated with **anti-inflammatory properties** by inhibition of the 5-lipoxygenase metabolite production and prostaglandin E2 (PGE2) cellular release, *(68-71)* as well as **sporicidal activity**, *(56, 70, 72, 73)*. It is associated with higher sporicidal efficacy than fluconazole and bifonazole against Microconidia and Chlamydospores, and a better sporicidal profile against Chlamydospores and Blastospores than terbinafine. *(56)* This is significant because the formation of fungal spores may contribute to the unsatisfactory cure rates and elevated risk of recurrence that can be associated with onychomycosis. *(56)*

In addition, ciclopirox is a well stablished antifungal agent, with over 30 years of expert experience in its use for the treatment of fungal infections. *(68)*

7.2. Hydroxypropyl Chitosan (HPCH)

Drug penetration in the nail is key for treatment success, but difficult to achieve due to the thickness of the nail plate and treatment-related factors, such as molecular size and lipophilicity of active ingredients. Therefore, topical formulations for onychomycosis need to be developed keeping in mind the physicochemical factors that affect nail permeation and ensuring that efficacious fungicide concentrations reach the area of the nail infection.

Hydroxypropyl Chitosan (HPCH) is a technology is based on a **hydrosoluble semisynthetic amino-polysaccharides biopolymer** with high compatibility with human tissues and an excellent safety profile. *(74-76)*

HPCH penetrates into intercellular spaces, holes and ridges of the nail surface, providing **physical support and smoothing the nail lamina,** it increases nail hardness and resistance to rupture**;** and can **reinforce the nail structure** and **prevent** the **establishment of new or recurring fungal infections** with repeated applications, helping to prevent further damage and cracking, which could otherwise enable the fungus to spread or reinfect treated areas. *(77, 78)* It also increases the drugs nail permeation, strengthening the efficacy of antifungal agents. *(79)* HPCH has been shown to protect the nail from fungal invasion even when not combined with any active substance. (Figure 1, Figure 2, Figure 3 and Figure 4).

Due to its high solubility in water, high plasticity and affinity to keratin, when applied to the nail surface, HPCH forms a film which acts as a **physical barrier against further fungal invasion and proliferation**. *(80, 81)* In addition, HPCH allows the antifungal active principle (ciclopirox) to remain in contact with the nail surface long enough for substantial penetration into and through the nail. *(74)*

HPCH also improves the patient's experience due to its easy application and removal, as it doesn't need chemicals or abrasives (e.g., nail filing) to remove previous application layers and can easily be removed by water, *(82)* as opposed to water-insoluble lacquers, which require solvent or abrasives to be removed, procedures that damage the nail structure and render it more prone to reinfection. *(77)* Therefore, ciclopirox 8% HPCH hydrolacquer easy removal process can protect the integrity of the nail structure. *(82)*

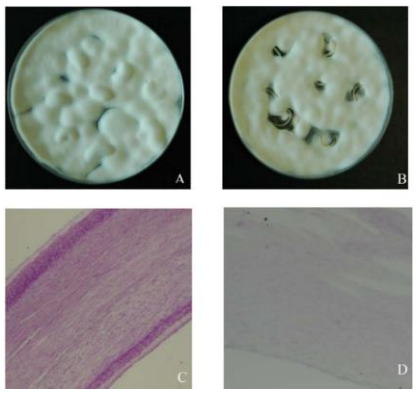

Figure 1. Trichophyton rubrum following 7 days of incubation.

Notes: Fungal growth on untreated (A) and treated nails (B). Fungal invasion of the nails of untreated (C) and treated (D) nails (100X; PAS stained). Figures from Bulgheroni et al. *(75)*

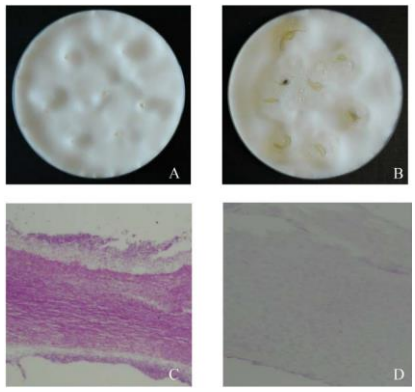

Figure 2. Trichophyton mentagrophytes following 7 days of incubation.

Notes: Fungal growth on untreated (A) and treated nails (B). Fungal invasion of the nails of untreated (C) and treated (D) nails (100X; PAS stained). Figures from Bulgheroni et al. *(75)*

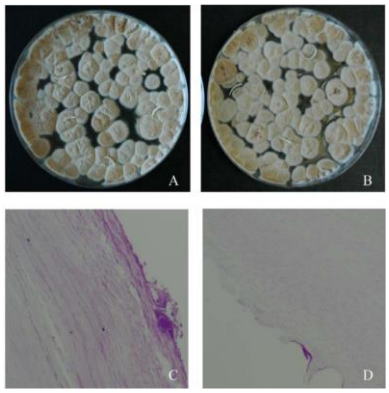

Figure 3. Scopulariopsis brevicaulis following 7 days of incubation.

Notes: Fungal growth on untreated (A) and treated nails (B). Fungal invasion of the nails of untreated (C) and treated (D) nails (100X; PAS stained). Figures from Bulgheroni et al. *(75)*

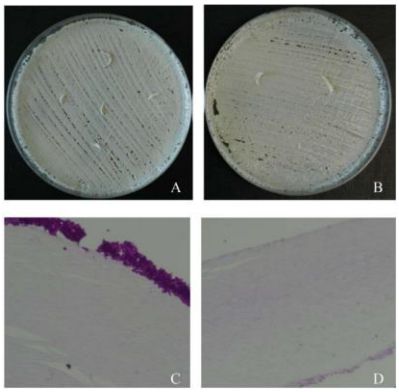

Figure 4. Candida parapsilosis following 7 days of incubation.

Notes: Fungal growth on untreated (A) and treated nails (B). Fungal invasion of the nails of untreated (C) and treated (D) nails (100X; PAS stained). Figures from Bulgheroni et al. *(75)*

7.3. Dosage Regimen and Duration of Treatment

Ciclopirox 8% HPCH hydrolacquer *(83)* is applied with the integrated bottle-cap brush in a thin layer once daily on the affected nail/s (fingernails, toenails and immediately adjacent skin) after washing with water and drying. The medicated nail hydrolacquer should be applied over the entire nail plate, 5 mm of surrounding skin and, if possible, under the free edge of the nail. It requires approximately 30 seconds to dry. The treated nails should not be washed for at least six hours, therefore, application in the evening before going to bed is recommended. After that time, normal hygienic practices can be followed. Ciclopirox 8% HPCH hydrolacquer doesn't require organic solvents or nail filing to be removed, it is sufficient to carefully wash the nails with water.

Treatment should be continued until complete mycological and clinical cure is achieved and the healthy nail has grown back. Normally, complete cure of fingernails is achieved in about 6 months, while toenails require from 9 to 12 months. The control of fungal culture should be done 4 weeks after the end of the treatment to avoid residues of active substance interfering with culture results.

7.4. Requirements to Ensure the Appropriate Use of Ciclopirox

Dose adjustments

No specific dose adjustments are required. Regular removal of the nail free edge and any onycholitic material by nail clipping is recommended.

Monitoring for safety

No systemic adverse effects exist with the ciclopirox medicated nail hydrolacquer due to its limited topical action. However, mild and transient local reactions at the application site have been reported. Very rarely, (< 1/10,000) have erythema, scaling, burning, and itching been

reported. Rash and eczema are other reactions with an unknown frequency. Transient nail discoloration has also been reported; however, this reaction could also be caused by onychomycosis itself.

Dosage modification for drug interactions

No interactions have been reported between ciclopirox and other drugs. No other forms of interaction have been reported.

Contraindications for the product are hypersensitivity to the active substance or to any of the excipients.

8. Review of Benefits and Harms

Ciclopirox 8% HPCH hydrolacquer has demonstrated *in vitro* and *in vivo* properties; efficacy an safety in the clinical development program compared to placebo, ciclopirox 8% water insoluble lacquer and amorolfine 5% lacquer; efficacy and safety in the real world clinical practice; and superiority in terms of efficacy when compared to other topical nail lacquers for onychomycosis treatment in a network meta-analysis (NMA) and Systematic Literature Reviews and Network Meta-Analysis

8.1.1. Cochrane Systematic Literature Review (SLR)

The 2020 Cochrane Systematic Literature Review (SLR) of topical and device-based treatments for fungal infections of the toenails *(84)* aimed to explore the evidence supporting these treatments in adults compared to placebo and each other. 56 studies were included in the review, which contained searches up to May 2019 and cumulatively included 12,501 participants who primarily had mild-to-moderate toenail onychomycosis. Most studies lasted between 48 to 52 weeks and were conducted in an outpatient setting.

Regarding topical treatments, ciclopirox 8% HPCH hydrolacquer and ciclopirox water insoluble lacquer were included in the SLR. Tavaborole and efinaconazole lacquers were also analyzed; however, since these drugs were not available during the ciclopirox 8% HPCH hydrolacquer clinical development program, no direct comparative data between ciclopirox 8% HPCH hydrolacquer and these newer treatments are available and thus the results for this treatments are not described.

Across two studies in 460 participants, evidence demonstrated that ciclopirox 8% water-insoluble lacquer may be better at producing complete cure (negative KOH and culture, and ≤ 10% area involvement of the target nail plate as determined by planimetry) and mycological cure (negative KOH and negative culture) compared to vehicle. However, it was also noted that ciclopirox lacquer may lead to an increase in the number of participants reporting AEs related to treatment, such as rashes and nail alterations. Though it was noted

that the evidence supporting these conclusions was low-quality, with the review concluding that the 95% confidence interval indicates makes little or no difference.

When the ciclopirox 8% HPCH hydrolacquer was compared to ciclopirox water insoluble lacquer or amorolfine lacquer in two studies of 490 participants, it was determined probable that ciclopirox hydrolacquer increased the complete cure rate (negative KOH microscopy + negative culture for fungal pathogens with no residual clinical involvement of the target toenail/100% growth of a healthy nail) relative to these comparators. No evidence indicating a difference in the number of AEs was reported.

Overall, when assessing complete cure, **moderate-quality evidence supports ciclopirox 8% HPCH hydrolacquer,** whereas low-quality evidence supports ciclopirox 8% water insoluble lacquer. For the newer tavaborole lacquer, effectiveness is supported by moderate-quality evidence, while high-quality evidence supports the recently available efinaconazole.

8.1.2. Network Meta-Analysis of Onychomycosis Treatments

The ***Gupta et al***. (2020) study analysed the relative efficacy of onychomycosis treatments using a network meta-analysis (NMA). *(85)* The NMA included 19 randomized controlled trials with a parallel-group design and a minimum of 48 weeks study duration.

Analysed treatments included oral itraconazole, fluconazole and terbinafine; topical ciclopirox (water-insoluble) and amorolfine lacquers, and topical terbinafine, tavaborole and efinaconazole nails solutions. The NMA concluded that **ciclopirox 8% water insoluble nail lacquer,** alongside the rest of the topical treatments, are significantly **superior to placebo in terms of mycological cure** rate (odds ratio [OR] for Ciclopirox 0.24 (CI 0.12-0.44), and that ciclopirox 8% water insoluble nail lacquer is also **superior** to **amorolfine lacquer** (OR 0.92 [CI 0.28-3.23]) and **terbinafine nail solution** (OR 0.96 [CI 0.34-2.77]).

Although the NMA did not include ciclopirox 8% HPCH hydrolacquer, it included ciclopirox 8% water insoluble lacquer, amorolfine lacquer and placebo, all comparators of ciclopirox 8% HPCH lacquer in head-to-head trials. *(74, 86-88)* In those clinical trials, ciclopirox 8% HPCH hydrolacquer proved to be significantly superior to both lacquers (amorolfine and ciclopirox 8% water-insoluble) and placebo in terms of efficacy. The results are described in Section 8.4.

8.2. Real World Evidence (RWE)

The most recent evidence for ciclopirox 8% HPCH hydrolacquer comes from a RWE study conducted in the Spanish setting. *(89)*

a. Rationale and Objective

The efficacy and safety of ciclopirox 8% HPCH hydrolacquer in combination with different oral treatments (terbinafine, itraconazole, and fluconazole) were studied in the setting of real-world clinical practice in Spain.

b. Methods

This was a retrospective analysis of patients diagnosed with onychomycosis in three tertiary care hospitals in Spain. Evidence was retrieved from electronic health records through natural language processing and machine learning techniques.

c. Results

A total of 408 patients with onychomycosis diagnosis and treatment with ciclopirox 8% HPCH hydrolacquer in combination with oral therapy were included in the study.

The results show that the most frequent combination was ciclopirox 8% HPCH hydrolacquer + oral terbinafine (67.7%), followed by a combination with oral itraconazole (20.8%) and oral fluconazole (11.5%). More than half of the patients (59.1%) started the treatment with combination of topical ciclopirox 8% HPCH and oral therapy, while 27.9% started the treatment only with oral therapy and 13% started the treatment only with topical ciclopirox 8% HPCH.

The response to treatment (positive response 15.7%, presumed positive 59.8%) was unrelated to treatment synchronicity or type of oral antifungal agent. Time to response was superior to 4 months in all three subgroups: median time to response for ciclopirox 8% HPCH hydrolacquer in combination with terbinafine was 4.13 months (1.57; 6.62), 4.57 (1.81; 6.72) for combination with fluconazole and 4.62 (0.00; 5.97) for combination with itraconazole. The percentage of patients with positive and presumed positive responses were 85.1%, 81.2%, and 72.1% in those treated with fluconazole, itraconazole, and terbinafine, respectively.

Erythema (5.6%), diarrhea (4.9%) and fever (4.2%) were the most frequently registered potential AEs, and the occurrence was similar in all three subgroups.

d. Conclusion

Treatment combinations of ciclopirox 8% HPCH with terbinafine, itraconazole, and fluconazole were commonly used in the Spanish clinical practice setting and time to response was unrelated to the type of oral antifungal agent. The present findings provide valuable insights for physicians paving the way for better management of patients with onychomycosis.

8.3. In vitro and in vivo studies

Regarding the *in vitro* and *in vivo* properties, ciclopirox 8% HPCH hydrolacquer provides faster and larger penetration compared to **ciclopirox and amorolfine water insoluble formulations.** *(79, 80, 90-92)* In the *in vitro* experiments, ciclopirox 8% HPCH was associated

with faster and larger nail penetration vs the reference ciclopirox 8% water insoluble lacquer and amorolfine 5% lacquer, *(80, 90, 91)* providing sufficient levels to inhibit fungal growth for a prolonged period of time (30 hours) after application of the lacquer. This effect can be attributed to a particular affinity of HPCH for the membrane, resulting in intimate contact and strong adhesion of the HPCH lacquer to the keratin substrate. Ciclopirox 8% HPCH hydrolacquer was also associated with increases into the dermatophyte inhibition rings of ciclopirox, *(79)* better *in vivo* penetration and higher predicted efficacy when compared to water insoluble formulation of amorolfine. *(92)* Ciclopirox 8% HPCH hydrolacquer permeation and penetration were also greater than that of efinaconazole 10% topical solution when two commercial preparations of the drugs were compared. *(93)*

8.4. Clinical Development Program

A literature review was conducted across biomedical databases to retrieve all relevant evidence on ciclopirox 8% HPCH hydrolacquer clinical development program. The search was complemented with hand searches in the grey literature. The inclusion and exclusion criteria, search terms and PRISMA flow diagram are presented in Appendix I: Literature Review search terms and PRISMA flow diagrams

8.4.1. Ciclopirox 8% HPCH is more active and better tolerated than reference Ciclopirox in the long-term treatment of onychomycosis

Ciclopirox 8% HPCH hydrolacquer is more active and better tolerated than reference ciclopirox 8% water insoluble lacquer in the long-term treatment of onychomycosis.

Ciclopirox 8% HPCH hydrolacquer is proven to be statistically more effective in treating mild-to-moderate onychomycosis compared to placebo at week 48 and statistically more effective than both placebo and water-insoluble ciclopirox 8% lacquer at week 60 in terms of complete cure rate, a composite efficacy endpoint difficult to achieve (100% clear nail, negative KOH microscopy, and negative culture).

Ciclopirox 8% HPCH hydrolacquer is also proven to be significantly superior to placebo at week 48 in rate to conversion culture and response rate, and significantly superior to both placebo and reference ciclopirox 8% water-insoluble lacquer in terms of response rate at week 60.

Its safety profile is better than that of the reference water insoluble lacquer.

8.4.1.1. Ciclopirox 8% HPCH Hydrolacquer has proven effective in comparison to reference Ciclopirox 8% water-insouble lacquer

a. Rationale and Objective

An innovative technology for nail drug delivery using HPCH was developed. HPCH is a water-soluble biopolymer acting as a film-forming agent. This led to the creation of an 8% ciclopirox HPCH hydrolacquer (P-3051), which demonstrated superior keratin affinity, nail permeation, and ease of use than the reference ciclopirox water-insoluble lacquer. *In vitro* studies showed enhanced antifungal efficacy, and its water-rinse removal and no need for nail filing make it favourable for long-term patient compliance.

The objective of this study was to assess the efficacy and safety of P-3051 (ciclopirox 8% HPCH hydrolacquer) vs. the market ciclopirox 8% water insoluble lacquer and placebo. *(86)*

b. Methods

This was a multicentre, 3-arm controlled, randomised clinical trial of ciclopirox 8% HPCH hydrolacquer vs. matching vehicle (placebo, double blinded) and vs. ciclopirox 8% water insoluble formulation (reference drug, blinded evaluator).

All lacquers were applied daily. Ciclopirox 8% HPCH hydrolacquer and placebo were removed by water, with no nail filing necessary, while ciclopirox 8% water insoluble formulation (reference drug) needs to be removed once a week with nail filing and alcohol, thus, treatment was double blinded for the first two drugs and blinded only for the evaluator for the reference water insoluble ciclopirox 8% lacquer. The final evaluation of the primary and secondary clinical endpoints was centrally made in blind by the International Study Coordinator, who acted as blinded evaluator.

Eligible participant where patients with distal subungual, mild-to-moderate dermatophyte onychomycosis of at least one big toenail (target nail) and an infected area ≥ 25% and ≤ 60% of target nail.

The study consisted of a 4–8 weeks run-in (culture of the nails was obtained), followed by 48 weeks of treatment, 4 weeks for washout and 8 weeks for follow-up.

The primary endpoint was complete cure (conversion to negative of both KOH microscopy and fungal culture, and 100% growth of a healthy nail) at week 48 (end of treatment) and confirmed at week 52 (washout).

Secondary endpoints were: 1) responders (conversion to negative of both KOH microscopy and fungal culture and decrease of diseased nail area to ≤ 10% [including zero] of total as assessed by the blinded evaluator); 2) conversion to negative of culture; and 3) growth rate of healthy nail.

The statistical design included a non-inferiority comparison between ciclopirox 8% HPCH hydrolacquer and the reference ciclopirox 8% water-insouble lacquer, with 80% statistical power; and a superiority comparison of ciclopirox 8% HPCH hydrolacquer over placebo, with 85% statistical power; in hierarchical order. Switching from a non-inferiority to a superiority hypothesis did not require additional statistical analysis. Superiority was directly tested using

the confidence limits from the non-inferiority objective. If the 95% CI for the treatment difference was entirely above both –10% and zero, this indicated statistical evidence of superiority of ciclopirox 8% HPC hydrolacquer over the reference water insoluble ciclopirox 8% lacquer at the 5% significance level (P < 0.05).

The safety variables included overall safety, AEs recording, vital signs and routine laboratory parameters, and specific evaluation of the local irritation potential.

c. Results

Population

A total of 467 patients from 24 centres (France, Germany, Italy, Czech Republic, Latvia, Poland) were randomized to receive ciclopirox 8% HPCH hydrolacquer (n=182), water insoluble ciclopirox 8% lacquer (reference drug) (n=188) or placebo (n=97). Approximately 1/5 of the patients had severe onychomycosis: patients with proximal involvement and/or > 60–100% affected nail area at baseline were 40 (22.1%) in the ciclopirox 8% HPCH hydrolacquer group, 38 (20.2%) in the reference drug group (water-insoluble ciclopirox 8% lacquer) and 20 (20.6%) in the placebo group. The three groups were similar with respect to sex, age and weight. 63.3% of patients were females, with a mean age of 49.84 years and a mean weight of 75.16 Kg. All patients were Caucasian and had a mean of 4.17 infected nails with a mean of 44.1% of the nail affected. This is consistent with a population of moderately to severely affected patients.

Efficacy

Complete cure rate (primary efficacy measure): complete cure rate was 5.7% the for ciclopirox 8% HPCH hydrolacquer group, 3.2% for the reference water insoluble ciclopirox 8% lacquer (reference drug) and 0% for placebo at week 48 (confirmed at week 52), with statistically significant differences (p = 0.0165 ciclopirox 8% HPCH hydrolacquer vs placebo). The results were confirmed at week 60 (Table 3 and Figure 5).

During the treatment period, ciclopirox 8% HPCH hydrolacquer results were superior to placebo and not inferior to water insoluble ciclopirox 8% lacquer (reference drug), with a consistent trend to superiority for ciclopirox 8% HPCH vs. reference drug.

At the end of follow-up (week 60) ciclopirox 8% HPCH was clinically and statistically superior to reference water insoluble ciclopirox 8% formulation (119% higher for cure rate, p<0.05).

Table 3. Complete cure rate results

Complete cure rate	48 weeks (confirmed at week 52)	60 weeks
Ciclopirox 8% HPCH hydrolacquer	5.7%	12.7%

Ciclopirox 8% water insoluble lacquer (reference drug)	3.2% (p=0.6834)†	5.8% (p<0.05)†,‡
Placebo	0% (p=0.0165)*	1.3% (p=0.0029)*

Notes: *Fisher exact test for the planned comparison ciclopirox 8% HPCH hydrolacquer vs. placebo; †Risk difference with associated two-sided 95% confidence interval; ‡Superiority comparison P-3051 vs. reference (Fisher exact test). | Acronyms: HPCH: Hydroxypropyl Chitosan.

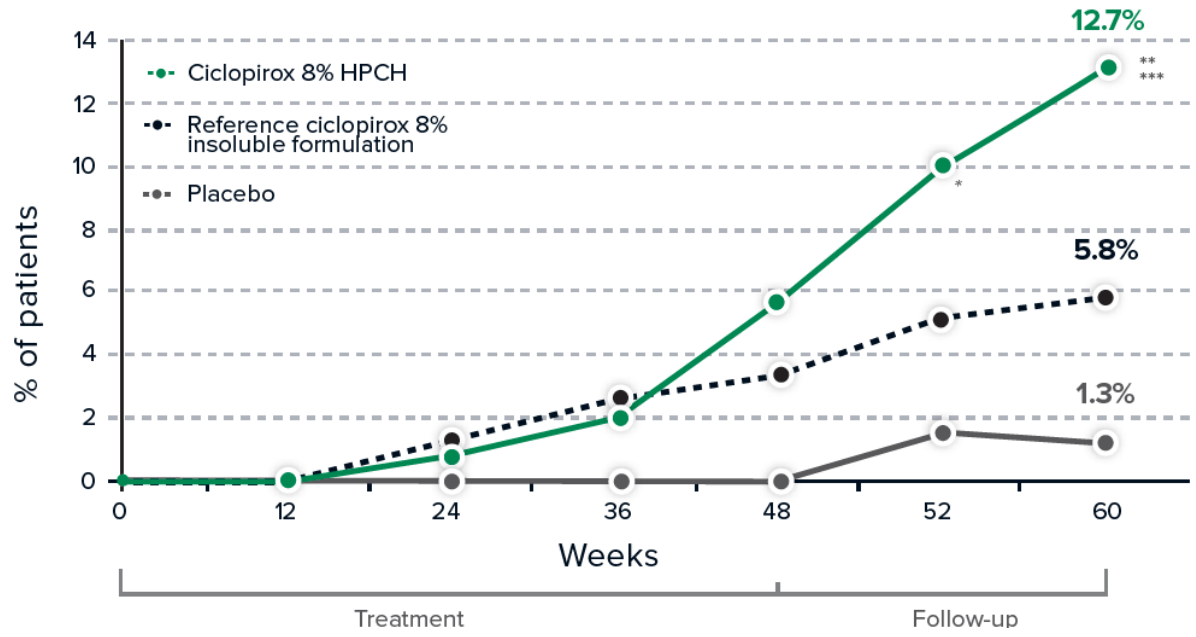

Figure 5. Complete cure rate during the active treatment period and follow-up

Notes: *Ciclopirox 8% HPCH vs. placebo p-value = 0.0143; **Ciclopirox 8% HPCH vs. placebo p-value = 0.0029; *** Ciclopirox 8% HPCH vs. reference ciclopirox p-value < 0.05 for the superiority comparison. | Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Baran et al. 2009. (86)*

Responders (response rate): response rate was 24% for the ciclopirox HPCH 8% hydrolacquer group, 17.3% % for the reference water insoluble ciclopirox 8% lacquer and 6.4% for placebo at week 48, with statistically significant differences (p = 0.0002 ciclopirox 8% HPCH hydrolacquer vs placebo). The results were confirmed at week 60 (Table 4 and Figure 6).

At the end of follow-up (week 60), ciclopirox 8% HPCH was clinically and statistically superior to reference ciclopirox 8% water insoluble formulation (66% higher for response rate) and placebo.

Table 4. Response rate results

Response rate	48 weeks	60 weeks
Ciclopirox 8% hydrolacquer HPCH	24%	28.7%
Ciclopirox 8% water insoluble lacquer (reference drug)	17.3% (6.7)†	17.3% (p<0.05)†,‡
Placebo	6.4% (p=0.0002)*	14.7% (p=0.0217)*

Notes: *Fisher exact test for the planned comparison Ciclopirox 8% HPCH hydrolacquer vs. placebo; †Risk difference with associated two-sided 95% confidence interval; ‡Superiority comparison P-3051 vs. reference (Fisher exact test). | Acronyms: HPCH: Hydroxypropyl Chitosan.

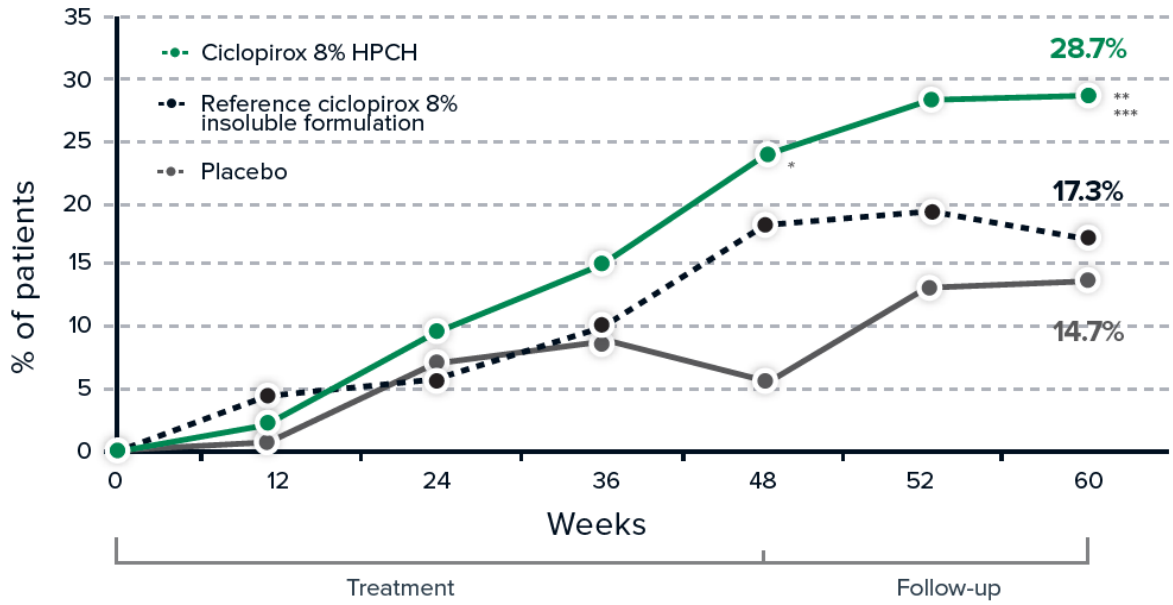

Figure 6. Responder rate during the active treatment period and follow-up

Notes: *Ciclopirox 8% HPCH vs. Placebo p-value = 0.0002; **Ciclopirox 8% HPCH vs. placebo p-value = 0.0217; ***Ciclopirox 8% HPCH vs. Ciclopirox reference p-value < 0.05 for the superiority comparison. | Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Baran et al. 2009. (86)*

Conversion to negative culture rate: the rate was 77% for ciclopirox 8% HPCH hydrolacquer, 77% % for the reference water insoluble ciclopirox 8% lacquer (reference drug) and 48% for placebo at week 12, with statistically significant differences between ciclopirox 8% HPCH hydrolacquer and placebo at weeks 48 and 52 (Table 5).

The conversion to negative of the mycology culture with ciclopirox 8% HPCH or reference ciclopirox 8% water insoluble formulation was quick, and this performance was maintained until the end of treatment.

Table 5. Conversion to negative culture rate results

Conversion to negative culture rate	12 weeks	48 weeks	60 weeks
Ciclopirox 8% hydrolacquer HPCH	77%	89.1%	79%
Ciclopirox 8% water insoluble lacquer (reference drug)	77%	90.8% (-1.7)†	79.7% (-0.8)†
Placebo	48%	69.1% (p=0.0001)*	72.4% (p=0.3204)*

Notes: *Fisher exact test for the planned comparison Ciclopirox 8% HPCH hydrolacquer vs. placebo; †Risk difference with associated two-sided 95% confidence interval. | Acronyms: HPCH: Hydroxypropyl Chitosan.

Growth rate of healthy nail: the weekly growth of healthy nail was +2.9‰ for ciclopirox 8% HPCH hydrolacquer, +1.9‰ for the reference water insoluble ciclopirox 8% lacquer and 0.7‰ for placebo, with statistically significant differences (p = 0.0015 ciclopirox 8% HPCH hydrolacquer vs placebo).

Ciclopirox 8% HPCH was more active than placebo in increasing healthy nail growth rate. This effect can be explained by the specific affinity of HPCH for nail keratin: positively charged HPCH adheres to the negatively charged keratin of the nail and penetrates the nail structure. *(70)*

It is worth mentioning that due to changes in keratin expression, the rate of growth is often decreased in the nails affected by onychomycosis. *(94, 95)* An effective antifungal agent needs to achieve and maintain sufficient drug concentrations throughout the complex nail unit during the growth of a healthy nail. *(96)*

Safety

Ciclopirox 8% HPCH was very well tolerated and devoid of any systemic side effects. Local symptoms and signs at the application site were all mild-to-moderate and 2 and 3 times less frequent with ciclopirox 8% HPCH than with the reference ciclopirox 8% water insoluble lacquer (Table 6). No serious or severe AEs were recorded in any of the study arms.

Table 6. Safety results

Adverse Events	Local symptoms (itching, burning, pain, erythema, others)	Local signs (definite oedema or erythema, minimal erythema)
Ciclopirox 8% HPCH hydrolacquer	7.8%	2.8%

Ciclopirox 8% water insoluble lacquer (reference drug)	16%	8.6%
Placebo	12.4%	7.2%

Acronyms: HPCH: Hydroxypropyl Chitosan.

d. Conclusion

Ciclopirox 8% HPCH formulation, besides being much easier to apply without needing any bothersome removal procedures, is more active and better tolerated than the reference ciclopirox 8% water-insoluble nail lacquer (and placebo) in the long-term treatment of onychomycosis.

8.4.1.2. A Post Hoc Analysis Proves the Efficacy Ciclopirox 8% HPCH Hydrolacquer In Mild-to-Moderate Onychomycosis

a. Rationale and Objective

The severity and percentage of nail involvement are usually considered the main prognostic factor for the treatment of onychomycosis.

The objective of the study was to evaluate the efficacy of P-3051 (ciclopirox 8% HPCH nail hydrolacquer technology) in a population subset of the pivotal study (modified intention-to-treat population of 302 patients, excluding severe disease [>50% nail involvement]) in line with recent onychomycosis pivotal trials *(87)*. Severe onychomycosis is usually treated with systemic treatment or a combination of systemic and topical treatments (see Section 9). *(97)*

b. Methods

The pivotal study has been described in this document as a prospective, randomized, parallel-group, three-arm study comparing P-3051 with reference water-insoluble ciclopirox and placebo (P-3051 vehicle) in 467 adults with onychomycosis (25-100% nail involvement) (see Section 8.4.1.1). *(87)*

For this post hoc analysis, the modified intention-to-treat (mITT) analysis dataset was a subset of the ITT dataset obtained by excluding patients with baseline nail involvement of > 50% and/or severe onychomycosis and/or age > 70 years. The safety population included the whole dataset of randomized patients.

The efficacy variables considered were complete cure rate (100% clear nail, negative KOH microscopy, and negative culture), response rate (≥90% clear nail, negative KOH microscopy, and negative culture), and culture conversion to negative, at the end of treatment (week 48) and at the end of follow-up (week 60). The clinical evaluation was double-blinded (P-3051 versus placebo) and investigator-blinded (P-3051 versus reference ciclopirox lacquer).

In this analysis, all three pairwise superiority contrasts were tested (i.e., P-3051 versus placebo, reference ciclopirox versus placebo, and P-3051 versus reference ciclopirox) using

the Fisher exact test, and considering the superiority comparison, P-3051 versus placebo, the primary one. In addition, two-sided exact 95% CIs for the difference in complete cure rates were calculated and reported for the three pairwise comparisons. Exact CIs were computed using the double binomial test implemented in the NCSS 2007 software.

Response rate and culture conversion to negative were analysed on the modified ITT set. The Pearson $\chi 2$ test was used to test the three pairwise comparisons, and risk differences in response rates were reported with their two-sided Wald 95% CIs.

A missing value at visit 7 (week 48, i.e., primary endpoint visit) was replaced with the last observation carried forward method, except for data missing for reasons related to treatment safety, which were filled in by default with the negative outcome.

c. Results

Population

A total of 302 patients of the ITT population (302/454, 66.5%) had baseline nail involvement ≤50%, mild-to-moderate onychomycosis, and age ≤70 years, and were thus included in the mITT population.

In this population subset, 34.1% had more than five onychomycotic nails, the mean proportion of target toenail involvement was 34.9% and the main pathogens were *T. rubrum* in 49.7% of patients and *T. mentagrophytes* in 40.1%.

Qualitative and quantitative demographic characteristics of the mITT population were homogeneously distributed over the three arms. Excluding a slightly greater prevalence of the number of toenails involved in the P-3051 group, the baseline data showed no differences between treatment groups.

Efficacy

Complete cure (primary endpoint analysis): P-3051 (Ciclopirox 8% HPCH hydrolacquer) was statistically superior to placebo in the complete cure rate after 48 weeks of active treatment (Fisher exact test, p = 0.028) (Figure 7). The complete cure rates were 7.6% in the P-3051 group, 3.3% in the reference ciclopirox group, and 0% in the placebo group.

At week 60 (end of follow-up), the complete cure rates were 15.1% in the P-3051 group, 5.8% in the reference ciclopirox group, and 1.6% in the placebo group. P-3051 was significantly superior to both placebo (p = 0.004) and reference ciclopirox (p = 0.021).

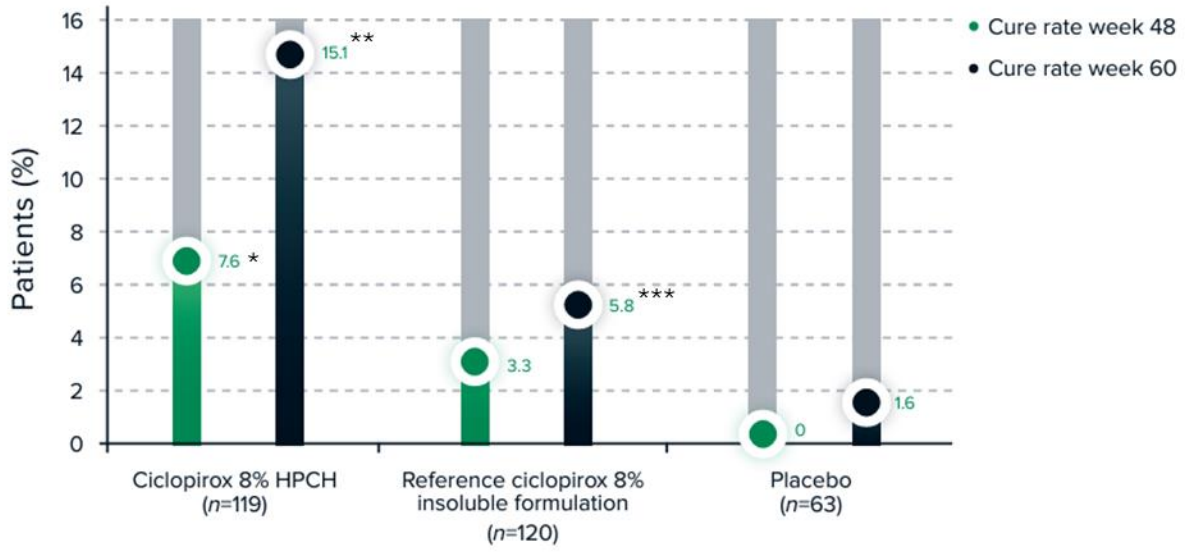

Figure 7. Complete cure rates at weeks 48 and 60

Notes: *Ciclopirox 8% HPCH vs. placebo, Fisher exact test, p = 0.028 (week 48); ** Ciclopirox 8% HPCH vs. placebo, p=0.004 (week 60); *** Ciclopirox 8% HPCH vs. reference water-insoluble ciclopirox 8%, p=0.021 (week 60). Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Piraccini B. et al., 2018. (87)*

Response Rates: At week 48, the response rates were 31.9% in the P-3051 group, 24.2% in the reference ciclopirox group, and 9.5% in the placebo group (Figure 8). At week 60, response rates were 34.5%, 20.8%, and 20.6% respectively. P-3051 was significantly superior to placebo at week 48 (p = 0.001) and the difference was close to significance at week 60 (p = 0.052). P-3051 was also significantly superior to reference ciclopirox at week 60 (p = 0.019).

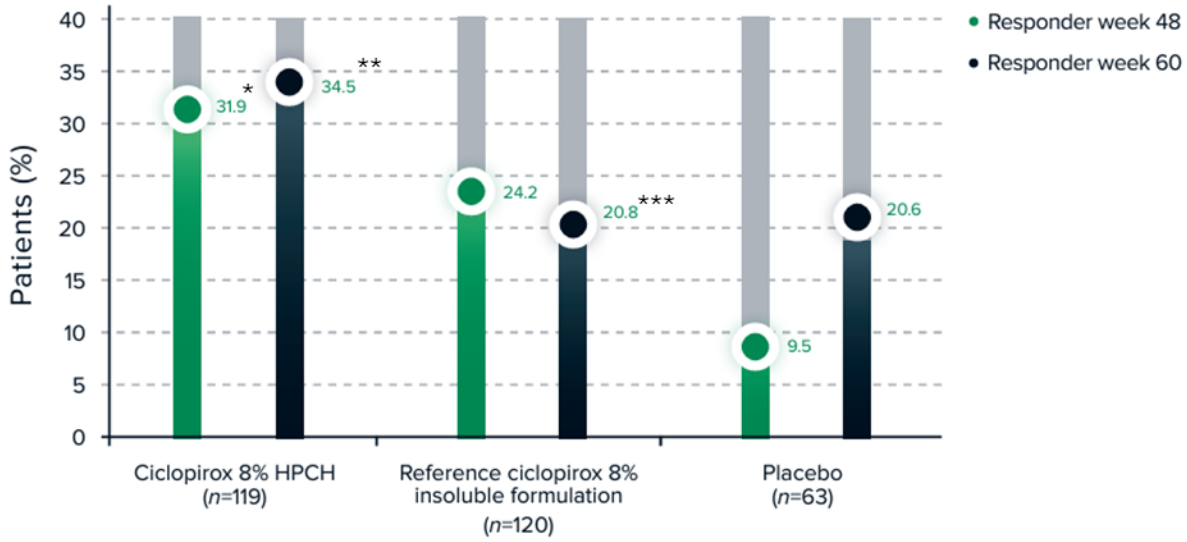

Figure 8. Response rates at weeks 48 and 60

Notes: *Ciclopirox 8% HPCH vs. placebo, p=0.001 (week 48); **Ciclopirox 8% HPCH vs. placebo, p=0.052 (week 60); ***Ciclopirox 8% HPCH vs. reference water-insoluble ciclopirox 8%, p=0.019 (week 60). | Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Piraccini B. et al., 2018. (87)*

Culture Conversion to Negative: Negative culture rates at week 48 were 91.6% in the P-3051 group, 90% in the reference ciclopirox group, and 73% in the placebo group (Figure 9). At week 60, the rates of negative culture were 82.4, 75, and 76.2%, respectively. P-3051 was significantly superior to placebo at week 48 (p = 0.001).

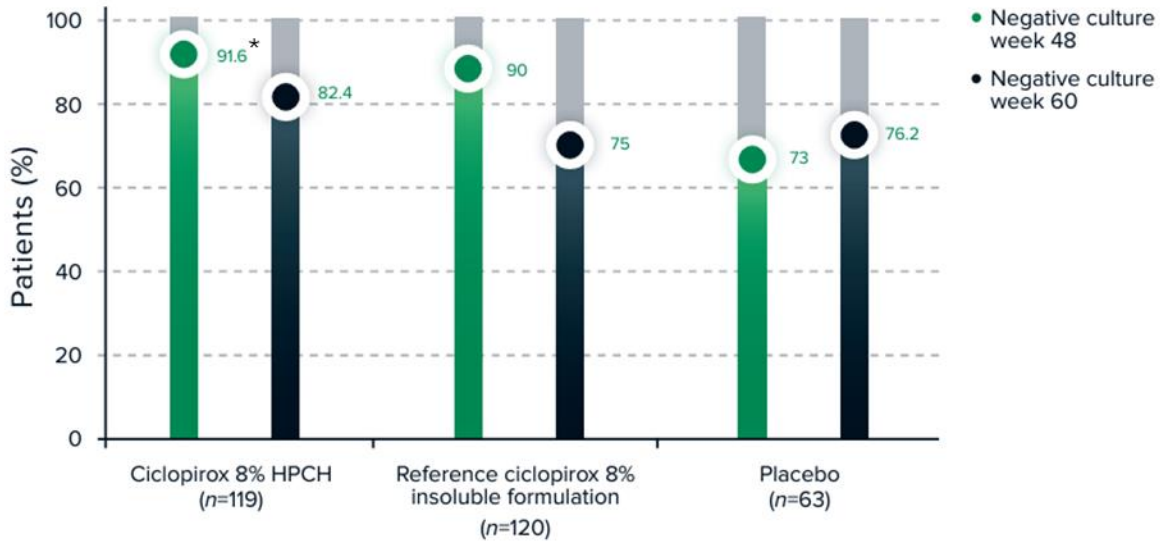

Figure 9. Culture conversion to negative at weeks 48 and 60

Notes: * Ciclopirox 8% HPCH vs. placebo, p=0.001 (week 48). | Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Piraccini B. et al., 2018. (87)*

Safety

Safety population of the post hoc analysis was identical to that of the pivotal study, therefore the were no differences from those of the original evaluation. The analysed treatments were generally safe, with a better safety profile in the P-3051 group, as previously reported

d. Conclusion

The significant superiority of ciclopirox 8% HPCH hydrolacquer over placebo and reference ciclopirox 8% water insoluble formulation was maintained in almost all parameters considered, even though the size of the subset and the statistical power were lower. Ciclopirox 8% HPCH was better tolerated than the reference water insoluble lacquer, in addition to being more active.

This analysis confirms that the severity of onychomycosis is a prognostic factor for responsiveness to antifungal treatments and that this can significantly affect reported efficacy data. The different inclusion criteria should be taken into account when reviewing the efficacy of antifungal agents.

8.4.2. Ciclopirox 8% HPCH is proven to be more effective in treating mild-to-moderate onychomycosis than other nail lacquers

When compared with amorolfine 5% lacquer, ciclopirox 8% HPCH hydrolacquer has a significantly higher efficacy for treating mild-to-moderate onychomycosis in terms of complete cure rate, treatment success, complete cure of infection and mycological cure with an infected nail area ≤ 75%. It is well-tolerated with no serious treatment-related AEs.

Ciclopirox 8% in HPCH hydrolacquer is also effective in cases of onychomycosis that persist despite treatment with amorolfine nail lacquer. This makes ciclopirox 8% HPCH a potential alternative to oral antifungal therapy after failure of topical amorolfine.

8.4.2.1. A Randomized Clinical Trial Proves a Significantly Superior Efficacy Ciclopirox 8% HPCH Hydrolacquer Against Nail Lacquer Amorolfine

a. Rationale and Objective

Topical nail lacquers are recommended for the treatment of mild-to-moderate onychomycosis as they minimize drug exposure, drug interactions and AEs when compared to systemic treatment.

The objective of the study was to compare the efficacy and safety of the nail lacquer P-3051 (ciclopirox 8% HPCH hydrolacquer) with amorolfine 5% lacquer for the treatment of mild-to-moderate toenail onychomycosis. *(74)*

b. Methods

This randomized (1:1), controlled, open label, parallel-group study evaluated the efficacy and safety of ciclopirox 8% HPCH hydrolacquer (daily application) versus amorolfine 5% lacquer (twice a week application) in patients with mild-to-moderate onychomycosis caused by dermatophytes, yeasts, or moulds.

Eligible participants were adults aged 18 to 75 with mild-to-moderate toenail distal lateral subungual onychomycosis (infected target nail area ≥ 25 and ≤ 75%) caused by dermatophytes, yeasts and moulds, affecting at least one big toenail (target nail) and without the presence of yellow spikes, dermatophytoma or lunula involvement. Exclusion criteria included severe plantar *Tinea pedis*, other nail conditions, or prior treatment use. Participants were not blinded to the treatment due to the different application schedules and removal procedures of the treatments. A blinded evaluation methodology was used to avoid the potential bias of an open-label design.

The study included a 4–5 week run-in period to obtain culture results, followed by a 48-week treatment period.

The primary variables were complete cure rate (negative KOH microscopy + negative culture for fungal pathogens + no residual clinical involvement of the target toenail), treatment success (negative KOH microscopy + negative culture for fungal pathogens + ≤ 10% residual involvement of the target toenail) and mycological cure (negative direct microscopy + negative culture), evaluated at different time points in the ITT population.

The number needed to treat (NNT), the number of patients who need to be treated for one to benefit compared with a control, was calculated. Since the trial had no placebo group, a 'putative' estimate of placebo effect was calculated using data gathered from vehicle-controlled studies (without ciclopirox 8% HPCH hydrolacquer), with a pooled cure rate in the vehicle group of 2.11%, obtained by combining five studies. *(98-100)* Safety was assessed through the AEs recording by the investigator.

The statistical design was a superiority trial between the drug under study and the reference product (ciclopirox 8% HPCH hydrolacquer vs amorolfine 5% lacquer). The z test was used to assess the difference between the two treatments with respect to the proportion of treatment success and the proportion of completely cured cases at weeks 12, 24 and 48.

c. Results

Population

A total of 120 patients were randomized to receive ciclopirox 8% HPCH hydrolacquer (n=60) or amorolfine 5% lacquer (n=60). Both groups were homogeneous with respect to main baseline characteristic. Mean ages were 51.45 and 53.85 years for ciclopirox and amorolfine patients, respectively. A mean of 86.65% were Caucasian women, with 45.4% of the target nail infected, and fungal species were dermatophytes (75.0%), yeast (19.15%), and moulds (5.85%) (average of both treatment groups).

Efficacy

Complete cure: The number of patients cured at week 48 was 21 (35.0%) in the ciclopirox 8% HPCH hydrolacquer group and 7 (11.7%) in the amorolfine 5% lacquer group, resulting in a statistical superiority ($p < 0.001$) in favour of ciclopirox. At week 24, 9 patients (15.0%) in the ciclopirox 8% HPCH hydrolacquer group and 6 (10.0%) in the amorolfine 5% lacquer group were already cured, but the difference between the groups was not statistically significant ($p = 0.408$) at this time point (Figure 10**Error! Reference source not found.**).

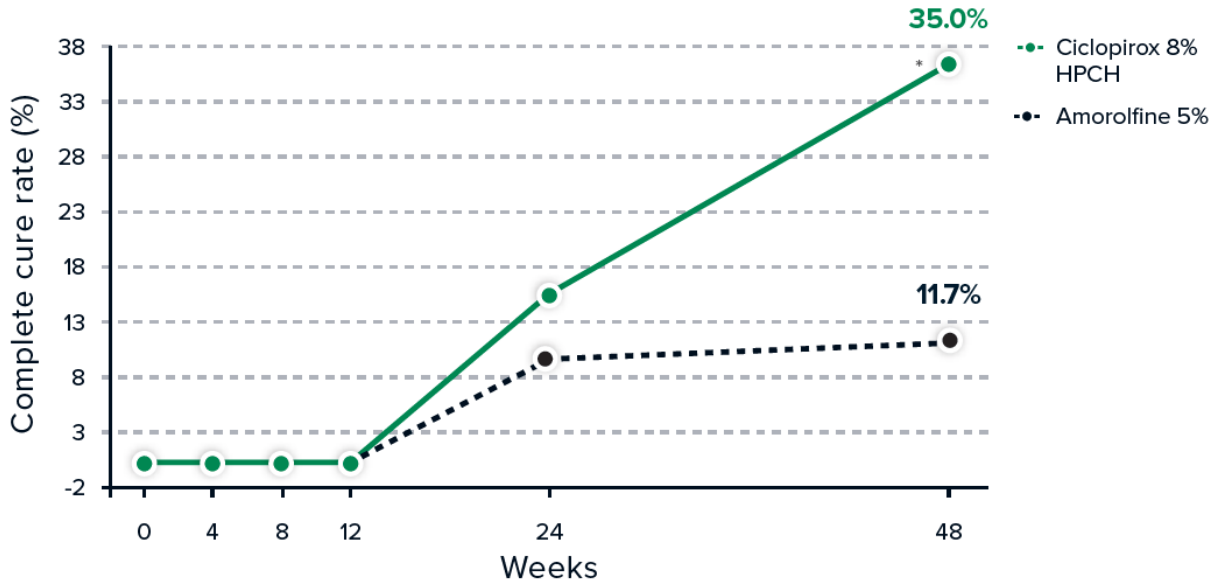

Figure 10. Complete cure rates of Ciclopirox 8% HPCH or amorolfine 5% treated patients

Notes: *p < 0.001. | Acronyms: HPCH: Hydroxypropyl Chitosan. | Adapted from *Iorizzo et al.* 2015. *(74)*

Treatment success: at week 48, 35 (58.3%) patients were considered successfully treated in the ciclopirox 8% HPCH hydrolacquer group vs 16 patients (26.7%) in the amorolfine 5% lacquer group ($p < 0.001$), resulting in a statistical superiority in favour of ciclopirox (Figure 11**Error! Reference source not found.**).

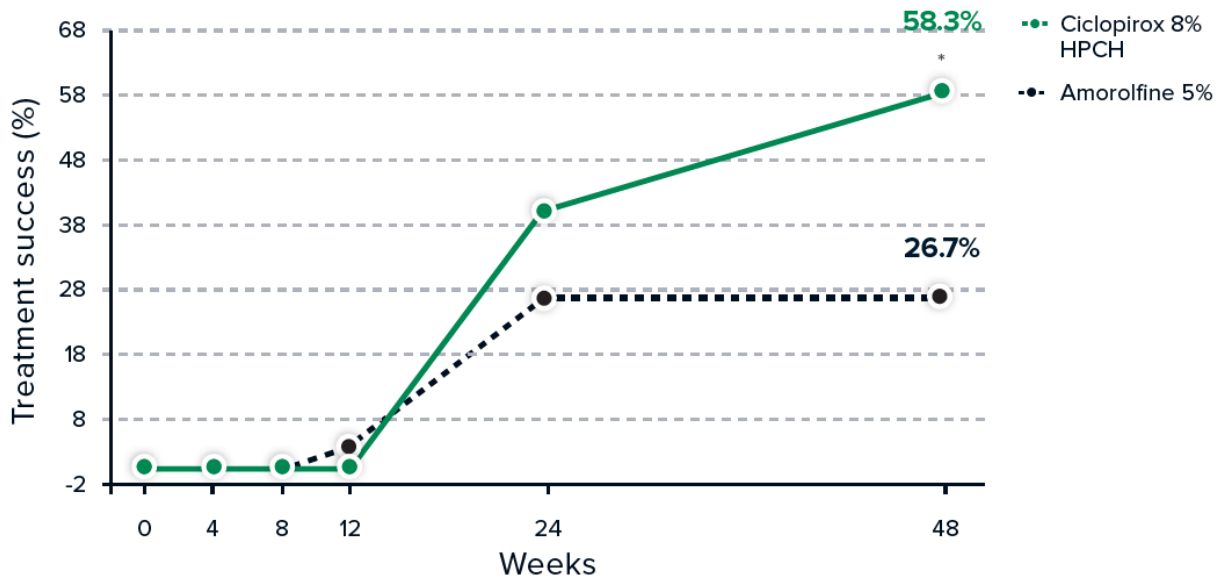

Figure 11. Treatment success rates of Ciclopirox 8% HPCH or amorolfine 5% treated patients.

Notes: *p < 0.001. | Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Iorizzo et al.* 2015. *(74)*

Mycological cure: At week 48, mycological cure was achieved in all 60 patients (100%) in the ciclopirox 8% HPCH hydrolacquer group, compared to 49 patients (81.7%) in the amorolfine 5% group. This difference was statistically significant ($p < 0.001$) in favour of ciclopirox. Mycological failure occurred in 18.3% of patients in the amorolfine 5% group, with 72.7% of those cases involving dermatophyte infections and 27.3% involving *Candida spp.* infections. At week 24, mycological cure was observed in 58 patients (96.7%) in the ciclopirox 8% hydrolacquer group and 52 patients (86.7%) in the amorolfine 5% group, again showing a statistically significant difference ($p < 0.05$) (Figure 12).

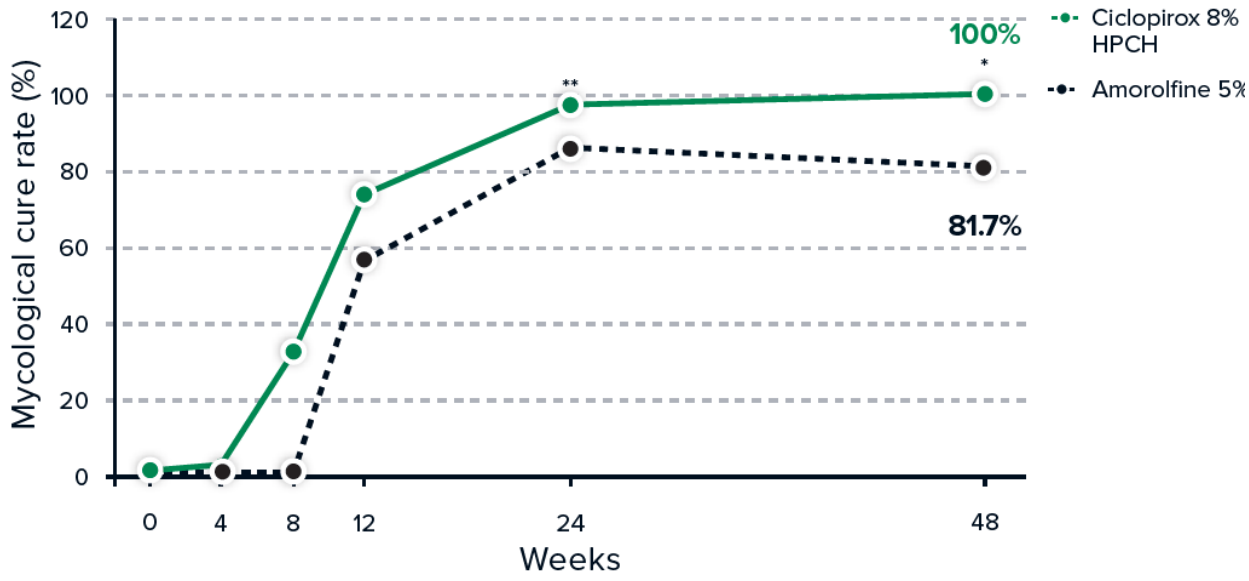

Figure 12. Mycological cure rates of Ciclopirox 8% HPCH or amorolfine 5% treated patients

Notes: *p < 0.001; **p < 0.05 | Acronyms: HPCH: Hydroxypropyl Chitosan. | Source: Adapted from *Iorizzo et al.* 2015. *(74)*

Number Needed to Treat (NNT): Ciclopirox 8% HPCH hydrolacquer is nearly four times more effective than amorolfine 5% lacquer: an average of 3 patients need to be treated with ciclopirox 8% HPCH hydrolacquer to achieve 1 cure, while 11 patients must be treated with amorolfine 5% to attain the same clinical outcome. This difference was statistically significant, showing superiority of ciclopirox 8% HPCH hydrolacquer compared to amorolfine 5%.

NNT in previous randomized European clinical trials: this additional analysis showed that ciclopirox 8% HPCH hydrolacquer is almost 6 times more effective than amorolfine 5% lacquer in complete cure of the infection, with non-overlapping 95% CI. The analysis was performed comparing evidence from the pivotal studies of *Baran et al. (86)* (ciclopirox 8% HPCH hydrolacquer pivotal trial), *Gupta et al. (100)* and *Elewski et al. (99)* (amorolfine 5% lacquer as reference, calculated using placebo of the test drug, and terbinafine nail solution) studies.

Safety

Both treatments were well tolerated without any safety concern. None of the patients in either group experienced serious AEs, AEs of severe intensity, treatment-related AEs, or any AEs that resulted in permanent discontinuation of treatment.

d. Conclusion

Ciclopirox 8% HPCH hydrolacquer is very efficacious and superior to amorolfine 5% in the treatment of mild-to-moderate onychomycosis in patients with an infected target nail area ≤ 75%.

8.4.2.2. Ciclopirox 8% HPCH Hydrolacquer has proven efficacy after topical treatment with amorolfine

a. Rationale and Objective

According to a recent controlled study, about 85% of patients with onychomycosis fail to respond to a standard treatment with amorolfine 5%. *(88)*

A noninterventional study of ciclopirox 8% HPCH hydrolacquer in non-responder patients to amorolfine aimed to verify whether a drug with an improved nail penetration, such as ciclopirox 8% HPCH lacquer (P-3051), can be useful in daily practice in those patients with persistent onychomycosis that failed to respond to a topical treatment with amorolfine. *(88)*

b. Methods

This noninterventional study (NIS) was conducted at 10 sites in Germany between June 2011 and January 2013.

Eligible patients were those with distal lateral subungual onychomycosis who had previously failed a topical treatment with amorolfine of at least 6 months and had terminated no more than one month before inclusion in the NIS. No concomitant oral treatments for onychomycosis were allowed.

Treatment failure in clinical or mycological outcome was defined as a positive KOH test with onychomycotic dystrophy leaving more than 10% of nail plate, in at least one toenail or one fingernail, chosen as target nail.

Participants included in the NIS were instructed to start the daily application of the P-3051 nail lacquer for 24 weeks and were evaluated at three visits. The enrolment evaluation was considered as the baseline time point (Visit 1), and the failure of previous treatments was proven clinically and by routine laboratory examination of nail-scrapings for mycological assessments (KOH test) and, optionally, the culture examination.

The primary outcome was the conversion to negative mycological findings (KOH and culture) at the end of treatment (Visit 3, 24 weeks). Secondary outcomes included clinical effectiveness rate, defined as composite of negative KOH microscopy, negative culture, and < 10% residual involvement of the target nail, as well as complete cure rate, defined as negative KOH microscopy, negative culture, and no residual clinical involvement of the target nail.

The Full Analysis Set (FAS) included all patients with at least one application of P-3051 and at least one visit with documentation of response data. Confirmatory analysis for robustness

was performed in the Per Protocol population (PP), defined as all patients who fulfilled the mandatory protocol procedures and had the KOH test available at the Visit 3.

c. Results

Population

A total of 70 patients were included in the FAS. Four patients prematurely discontinued after 12 weeks: out of these, 3 were lost to follow up and the last one abandoned due to an AE not related to study drug (broken leg). None of the enrolled patients was excluded from the efficacy analysis.

Culture was available at baseline in 48 patients: all were positive to dermatophytes, out of them 64.6% for *Trichophyton* spp. (*T. rubrum*/*T. mentagrophytes*), 20.8% for undefined dermatophytes and 8.3% for mixed fungi. Positivity for *Scopulariopsis brevicaulis*, undefined moulds or undefined yeasts was reported for one (2.1%) patient each. The average affected area of target nail at baseline was 38.1% with a standard deviation (SD) of 20.2%.

Efficacy

Negative KOH test rate

In the FAS analysis, the response rate to P-3051 treatment of the negative KOH test was 58.6%. This result was highly statistically significant ($p<0.0001$). The analysis on PP population confirmed the FAS set, since the primary endpoint was achieved by 62.1% of patients.

Complete cure Rate

The culture examination pre- and post-treatment was available in 28 patients. Out of these, the mycological culture was converted to negative in 25 patients (89%), while only in 3 patients it was not (10.7%). Furthermore, 17 out of those patients, were also negative to the direct KOH microscopic examination. Those patients, defined as “mycological cure”, (i.e. as negative microscopy and negative culture) were in proportion 60.7% of all patients with pre- and post- mycotic culture available ($p<0.0001$).

The complete cure rate (defined as composite of negative KOH microscopy and negative culture and no residual clinical involvement of the target toenail) was obtained in 10.7% of the patients ($p< 0.0001$).

Response rate (clinical effectiveness rate)

The percentage of responders, defined as negative KOH microscopy, negative culture and < 10% residual involvement of the target toenail (at least 90% healthy nail growth), was 21.4%, matching those patients where the decrease of the residual involvement of the target nail area was ≤ 5%.

Safety

No adverse drug reactions were reported during the period of the study.

d. Conclusion

The results suggest that ciclopirox 8% HPCH hydrolacquer may be effective in amorolfine treatment failures as an alternative prior to oral antifungal therapy, or in cases where oral antimycotics are contraindicated.

8.5. Ciclopirox & Anti-Fungal Resistance

8.5.1. Limited Onychomycosis Treatment Options Induces Anti-Fungal Resistance

Resistance to oral antifungals, such as terbinafine and azoles, is being increasingly recognized as an emerging challenge, with resistant yeast and mould species associated with systemic infections already categorized as a great threat to public health. *(64)* Resistant strains prolong disease duration, increasing the opportunity for disease transmission, thereby increasing infection rates and encouraging global disease spread. *(64)* Increasing the use of topical antifungals, such as ciclopirox has been noted as an option to circumvent antifungal resistance, especially as the nail plate has been increasingly recognized as limiting physical barrier to drug delivery.

Additionally, while documented cases of resistance quickly emerge following adoption of systemic antifungal, no natural dermatophyte resistance to topical antifungals has been noted, 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. Finally, it was noted that a combination treatment, which utilizes a topical treatment alongside an oral therapy, may reduce treatment failure caused by primary resistance and limit the development of a secondary resistance while also improving treatment adherence. *(64)*

Following a recent large outbreak of antifungal-resistant *Trichophyton indotineae* in India, resistant strains have also been identified sporadically throughout Europe, including France, Italy, Greece, Germany, Spain, Switzerland and Denmark. However, the true scope of the challenge is difficult to ascertain due to the lack of antifungal susceptibility testing. *(101)* Out of the 63 total cases reviewed, 61 were found to be resistant, with 94% of tested isolates (47/50) being reported as terbinafine-resistant. In a pilot study of dermatologists from 23 countries, many participants suggested using topical antifungals in combination with the oral treatment as an approach to overcome resistance. It was also noted that prolonged treatments with systemic azoles, which are the most frequent treatment when terbinafine resistance is suspected or confirmed, risks selecting resistant isolates and significant side effects such as kidney and liver injury. Instead, it was stated that topical agents may be preferable for relapsing patients with dermatophyte infections who require extended treatment. (X)

8.5.2. Ciclopirox's Low Propensity To Induce Anti-Fungal Resistance

In contrast to other topical antifungals for onychomycosis that target the ergosterol synthesis pathway, including terbinafine and azoles, ciclopirox has a unique mechanism of action which the pathogen is not able to adapt against by mutating the binding site of the targeted enzyme. Specifically, it is distinguished from therapeutic alternatives due to its chelatation of polyvalent metal cations, leading to the inhibition of many cellular activities and modifications to the fungal plasma membrane. This unique mechanism, which exhibits broad fungicidal activities, is indicative of a lower propensity for inducing antifungal resistance in the species which contribute to onychomycosis. An important factor to preventing the development of resistance is the ability of drugs with fungicidal activities to permeate the nail and reach the site of infection. In this regard, *in vitro* studies have demonstrated that the permeability of ciclopirox 8% HPCH hydrolaquer is about ten times greater than that of efinaconazole and significantly improved relative to their non-HPCH counterparts. *(93)* The authors also hypothesized that these results were also attributable to cliclopirox's ability to accumulate in the nail, enabling gradual release into both the nail plate and bed. Similarly, in contrast to terbinafine, itraconazole and amorolfine, where resistant straints were identified *in vitro*, no mutant resistance to ciclopirox was identified in *T. rubrum* strains. *(45)*

9. Summary of recommendations in current clinical guidelines

A literature review was conducted across biomedical databases to retrieve all relevant evidence on ciclopirox 8% lacquer (both water insoluble and HPCH lacquers) recommendations in clinical guidelines and scientific articles. The search was complemented with hand searches in the grey literature, including the webpages from the Ministry of Health of multiple countries, and scientific and patient association webpages. For the biomedical databases, search was restricted to a 10 year time frame to ensure that the most updated evidence was available for most of countries. For the hand searches, the time frame was extended to 25 years to allow for the inclusion of guidelines from a broader range of countries. The inclusion and exclusion criteria, search terms and PRISMA flow diagram are presented in Appendix I: Literature Review search terms and PRISMA flow diagrams

9.1. Recommendations in WHO guidelines

No onychomycosis specific guidelines have been published by the WHO.

However, the **Pan American Health Organization** (PAHO), part of the WHO, recently published the "Infectious Diseases Treatment 2024-2026. Ninth Edition" guideline, *(102)* which recommends oral treatment with terbinafine as the first option and itraconazole as an alternative for the treatment of onychomycosis of the feet or hands caused by

dermatophytes or non-dermatophyte moulds. Nevertheless, in the current WHO EML 23rd list (2023), oral terbinafine is not included and oral itraconazole is not specifically indicated for onychomycosis.

The **Index Medicus for South-East Asia Region** (IMSEAR), an **archive** of selected **publications** in **health sciences** in the **WHO South-East Asia** Region that includes formally published health science journals, health reports and documents, endorses an article about onychomycosis treatment. The ***Singal et al.*** "Onychomycosis: Diagnosis and management" 2011 review article *(103)* describes lacquers as specialized transungual drug delivery system, that ensure high concentration and prolonged contact of the active substance. It recommends topical monotherapy treatment for onychomycosis when:

1. Involvement is limited to distal 50% of nail plate, 3 or 4 nails are involved
2. No matrix area is involved
3. For superficial white onychomycosis (SWO)
4. As prophylaxis in patients with high risk of recurrence
5. When oral therapy is inappropriate
6. In children with thin, fast-growing nails

As part of the available topical treatments, **ciclopirox 8% lacquer** is described as a drug with broad spectrum against yeasts, dermatophytes, and non-dermatophytes moulds. **Ciclopirox 8% HPCH hydrolacquer** is highlighted as a new therapy that showed to be more effective than the conventional ciclopirox water insoluble lacquer. *(103)* It also describes others topical drugs like terbinafine and **highlights the potential of combination therapy** (oral + topical treatment). Combination therapy may allow reduction in oral dosing, resulting in increased patient tolerance and compliance, while **improving efficacy and reducing relapses**.

9.2. Recommendations in Non-Profit Organizations Guidelines

No specific guidelines for onychomycosis treatment from non-profit organizations where identified.

However, the 2024 "Clinical guidelines - Diagnosis and treatment manual" from **Doctors Without Borders** mentions that for onychomycosis caused by dermatophytes, treatment is prolonged (12-18 months with oral griseofulvin) and, in practice, difficult and commonly associated with **treatment failures** and **relapses.** *(104)*

The 2020 "Blue Book: A medical Guide for our Projects" from the **German Doctors** organization highlights the challenges in treating onychomycosis, noting that **treatment outcomes remain uncertain** even after several months of therapy with oral fluconazole or griseofulvin. *(105)*

9.3. Recommendations in Other Clinical Guidelines

The use of topical ciclopirox (both HPCH hydrolacquer and water insoluble lacquer) for the treatment of onychomycosis is recommended by a large number of international and national guidelines and scientific articles (Table 7).

Table 7. National and International Guidelines that recommend Topical Ciclopirox for the Treatment of Onychomycosis

Author/Organization	Country	Title	Publication date
Nail Society of India (NSI) *(106)*	India	Nail Society of India Recommendations for Treatment of Onychomycosis in Special Population Groups	2024
Nail Society of India (NSI) *(107)*	India	Nail Society of India (NSI) Recommendations for Pharmacologic Therapy of Onychomycosis	2023
Association of the Scientific Medical Societies of Germany (AWMF) *(97)*	Germany	S1 Guideline Onychomycosis	2023
American Academy of Family Physicians (AAFP) *(108)*	US	Topical and Device-Based Treatment of Toenail Onychomycosis	2021
Spanish Society of General and Family Physicians (SEMG) *(109)*	Spain	Dermatological Training in Primary Care	2020
Ministry of Health *(110)*	Peru	Clinical Practice Guidelines of the Dermatology Department	2019
Spanish Society of Family and Community Medicine (SEMFYC) *(111)*	Spain	Onychomycosis	2018
British Association of Dermatologists (BAD) *(112)*	UK	BAD Guidelines for the Management of Onychomycosis 2014	2014
National Health System *(113)*	Spain	Onychomycosis: Diagnosis and Treatment	2008
Gupta et al. *(64)*	Canada, US	Treatment of onychomycosis in an era of antifungal resistance: Role for antifungal stewardship and topical antifungal agents	2024
Yousefian et al. *(114)*	US	Treatment Options for Onychomycosis: Efficacy, Side Effects, Adherence, Financial Considerations, and Ethics	2024

Author/Organization	Country	Title	Publication date
Chakraborty et al. *(115)*	India	Therapeutic treatment strategies for the management of onychomycosis: a patentperspective	2023
Ibrahim Elsayed et al. *(116)*	Egypt	Treatment Options of Onychomycosis: Review Article	2023
Gupta et al. *(117)*	US	Onychomycosis in Older Adults: Prevalence, Diagnosis, and Management	2022
Gupta et al. *(118)*	Global	A Paradigm Shift in the Treatment andManagement of Onychomycosis	2021
Lacourt et al. *(119)*	Chile	Management of onychomycosis in adults in Primary Care	2020
Vikas et al. *(120)*	India	Mechanistic Insights of Formulation Approaches for the Treatment of NailInfection: Conventional and Novel Drug Delivery Approaches	2020
Gupta et al. *(121)*	Canada	Emerging drugs for the treatment of onychomycosis	2019
Lindblad et al. *(122)*	Canada	Putting the fun in fungi: toenail onychomycosis	2019
Kovitwanichkanont et al. *(123)*	Australia	Superficial fungal infections	2019
Lipner et al. *(124)*	United States	Onychomycosis: Treatment and prevention of recurrence	2019
Gupta et al. *(53)*	Global	Global perspectives for the management of onychomycosis	2019
Christenson et al. *(125)*	Australia	Challenges and Opportunities in the Management of Onychomycosis	2018
Gupta et al. *(126)*	Canada	Management of Onychomycosis in Canada in 2014	2014
Singal et al. *(103)**	South-East Asia	Onychomycosis: Diagnostic and Management	2011
Ballesté et al. *(127)*	Uruguay	Onychomycosis. Review of the topic	2003
Canadian Skin Patient Alliance *(128)*	Canada	Your Complete Guide to Toenail Fungus Infections	Not available

Notes: *The article is part of the Index Medicus for South-East Asia Region (IMSEAR), an archive of selected publications in health sciences in the WHO South-East Asia Region | Acronyms: AAFP: American Academy of Family Physicians; AWMF: Association of the Scientific Medical Societies of Germany; BAD: British Association of Dermatologists; CFPC: The College of Family Physicians of Canada; IMSEAR: Index Medicus for South-East Asia Region; NSI: Nail Society of India; SemFYC: Spanish Society of Family and Community Medicine; SEMG: Spanish Society of General and Family Physicians; WHO: World Health Organization.

Onychomycosis treatment guidelines are available worldwide. Associations and institutions such as the Nail Society of India, the Association of the Scientific Medical Societies in Germany, the American Academy of Family Physicians, the American Academy of Dermatology, the Spanish Society of Family and Community Medicine, the Spanish Society of General and Family Physicians, the British Association of Dermatologists, and the Ministries of Health from Peru and Spain have issued clinical guidelines and recommendations for the treatment of onychomycosis that include ciclopirox 8% lacquer as part of the recommended therapies.

Guidelines and consensus

The **Association of the Scientific Medical Societies of Germany** (AWMF) recommends topical treatment (**including water insoluble ciclopirox water-insoluble lacquer and HPCH hydrolacquer**) for mild to moderate nail infections (distal subungual onychomycosis and SWO, with max. 40% of the nail surface affected and/or max. 3/10 toenails affected) caused by dermatophytes, yeasts, moulds and *Candida*; and for **long-term antifungal prophylaxis after successful onychomycosis treatment**. Regarding **ciclopirox 8% HPCH hydrolacquer**, it highlights the water-soluble **HPCH biopolymer**, which by binding to nail keratin, enables **better transport** and **release** of the active substance (ciclopirox) and **has an additional antibacterial effect**. Another advantage is that ciclopirox 8% HPCH hydrolacquer **can also be applied to the residual nail or nailbed**, especially after a traumatic nail removal by means of urea or a drill (2023). *(97)*

The **National Hospital "Arzobispo Loayza"**, under the **Peruvian Ministry of Health**, recommends using ciclopirox 8% lacquer alongside systemic treatment for onychomycosis to enhance the effectiveness of the systemic therapy (2019). *(110)*

The **Spanish Society of General and Family Physicians** (SEMG) recommends **ciclopirox 8% hydrolacquer** for the treatment of onychomycosis, emphasizing that the best option is the combined' approach of topical treatment with systemic therapy (2020), *(109)* and the **Spanish Society of Family and Community Medicine** (SemFYC) recommends ciclopirox 8% lacquer as an alternative treatment to amorolfine lacquer (2018). *(111)* The **Spanish National Health System** recommendations endorse the use of ciclopirox olamine for the treatment of onychomycosis for SWO and incipient lesions of the DLSO type affecting a single nail without matrix involvement caused by dermatophytes and for onychomycosis caused by yeasts, where topical treatment with ciclopirox lacquers is generally sufficient. Ciclopirox

is also useful in the treatment of onychomycosis caused by non-dermatophyte moulds, alone or in combination with systemic treatment (2008). *(113)*

The **British Association of Dermatologists** (BAD) recommends ciclopirox (strength of recommendation D; level of evidence 3[1]) for superficial and distal onychomycosis and for patients in whom systemic therapy is contraindicated. Systemic treatments received higher levels of evidence and strength of recommendation than all topical therapies. The BAD concludes that there is sufficient evidence to recommend combination therapy if response to topical monotherapy is likely to be poor. As pharmacoeconomic considerations, the experts suggested that cost of drug therapy may be taken into account when assessing the risk-to-benefit ratio of onychomycosis treatment, given that systemic drug therapy for onychomycosis is costly, as generally long treatment courses are required, especially for toenail onychomycosis. Future directions should focus, among others, on exploring combination therapies—whether systemic with topical or multiple systemic agents—aiming to improve efficacy and reduce drug-related AEs, and in further research to better understand drug resistance and poor patient compliance (2014). *(112)*

The **Nail Society of India** (NSI) recommends the use of ciclopirox olamine 8% nail lacquer as a monotherapy for patients in whom **topical therapy is indicated**, or **systemic therapy is contraindicated** (Level of Evidence, LOE-III, Grade of Recommendation, GOR-C) (Supplementary Table 5 and Supplementary Table 6), although it notes that ciclopirox lacquer as a monotherapy is associated with low compliance rates and therefore, limited efficacy. **Combination therapy** with different classes of drugs (including ciclopirox) has shown to **improve treatment outcomes**, therefore, it is recommended in patients with indications for systemic therapy (GOR-A). **Ciclopirox** (GOR-C) **may be used** for combination therapies. *(107)* Regarding the choice of topical therapy, it is recommended to base it on local availability and ease of application (GOR-D). Cost advantage between agents may be minor, considering varying frequency of application (GOR-D) (2023). (see Appendix II: **Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence and Grade of Recommendation**

In **special populations**, the **Nail Society of India** recommends topical treatment (including ciclopirox 8% lacquer) in the setting of SWO or mild to moderate DLSO without matrix involvement (LOE-III, GOR-B) (Supplementary Table 5 and Supplementary Table 6) for children. For pregnant and breastfeeding patients, **topical monotherapy with ciclopirox**

[1] Level of evidence 3: non-analytical studies (for example case reports, case series). Strength of recommendation D: Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+; or Formal consensus.

8% is the treatment of choice (LOE II, GOR B) and may be combined with mechanical or destructive modalities for pregnant women and mechanical or laser based modalities for breastfeeding women, avoiding systemic treatments (2024). *(106)*

The **American Academy of Family Physicians** (AAFP) recommends **ciclopirox 8% (HPCH hydrolacquer and water insoluble lacquer)** to treat mild to moderate onychomycosis. It considers ciclopirox 8% HPCH hydrolacquer to be supported by moderate-quality evidence and associated with **higher complete cure rates** compared to water insoluble ciclopirox 8% and amorolfine 5% lacquers, with no difference between these treatments in mycologic cure or risk of adverse effect (2021). *(108)*

Other articles

Other articles from the **US, Canada, Australia, Chile, India, Egypt, South-East Asia, and Global** recommend the use of **ciclopirox as a topical treatment for onychomycosis.**

The 2020 article by ***Lacourt A. et al.*** "Management of onychomycosis in adults in Primary Care" from the **Pontifical Catholic University of Chile** cites the *2014 BAD guidelines for the management of onychomycosis 2014* (UK) as the base for their recommendations and recommends ciclopirox 8% lacquer as topical treatment for onychomycosis, with higher mycological cure rates than amorolfine 5% lacquer (34% vs. 30%, respectively). *(119)*

The 2019 article by ***Kovitwanichkanont et al.*** "Superficial fungal infections" from the **Monash University (Australia)** recommends **ciclopirox 8% lacquer** (with debridement of hyperkeratotic nails) **when systemic treatment is contraindicated**. After therapy for onychomycosis, there may be a recurrence or reinfection rate of up to 25%, and topical treatment (including ciclopirox) can be used as **prophylaxis for prevention of recurrence**. *(123)*

The 2019 article by ***Lipner et al.*** "Onychomycosis Treatment and prevention of recurrence" from the Department of Dermatology of the **Weill Cornell Medicine (US)** recommends **topical drugs** (including **ciclopirox 8% lacquer**) for **onychomycosis treatment** due to the low risks of systemic side effects and drug-to-drug interactions, and the avoidance of laboratory monitoring. Topical treatment is specially recommended when there are contraindications to oral therapy, and as theoretical use (that needs further study) for more severe cases in combination with systemic medications or debridement, and for prevention of recurrences or reinfection. *(124)*

The 2019 article by ***Christenson et al.*** "Challenges and Opportunities in the Management of Onychomycosis" from the University of Canberra – **Australia,** recommends lacquers, including **ciclopirox 8% lacquer**, as topical treatments for mild – moderate cases of distal or superficial onychomycosis. Topical antifungals have the advantage of causing fewer and less serious side effects, and the disadvantages of long treatment periods, and limited efficacy due to poor nail plate penetration. *(125)*

The 2024 article by ***Gupta et al.*** "Treatment of onychomycosis in an era of antifungal resistance: Role for antifungal stewardship and topical antifungal agents" from the **Department of Medicine - University of Toronto** (**Canada**), highlights the advantages of topical treatment for onychomycosis (including ciclopirox 8% lacquer), being 1) it may avoid some aspects of clinical resistance, as they are not impacted by systemic metabolism or absorption into other tissues; 2) no drug–drug interactions have been reported; 3) concomitant medication use is unlikely to affect their efficacy in the long-term treatment of onychomycosis; and 4) topical antifungals are associated with fewer safety concerns, as no systemic AEs have been reported, and rates of serious local AEs are typically low. There are no reports of natural dermatophyte resistance to topical ciclopirox. *In vitro*, ciclopirox has demonstrated no liability for spontaneous or induced development of dermatophyte resistance. *(64)*

The 2023 review article by ***Chakraborty et al***. "Therapeutic treatment strategies for the management of onychomycosis: a patent perspective" from the **Chitkara University of India** highlights the difficulty treating onychomycosis, due to high percentage of treatment failures and reinfections. Nail lacquers incorporating ciclopirox and amorolfine help to decrease transonychial water loss and are effective in eradication of fungus for onychomycosis treatment. **Ciclopirox** nail lacquer has also been used due to its effect on nucleic acid and protein synthesis and its **anti-inflammatory** nature. *(115)*

The 2024 review article by ***Yousefian et al***. "Treatment Options for Onychomycosis: Efficacy, Side Effects, Adherence, Financial Considerations, and Ethics" from the **US** mentions ciclopirox 8% lacquer as broad-spectrum recommended antifungal for the treatment of mild onychomycosis cases, as an adjuvant to other treatments, and in patients in whom oral therapy is contraindicated. *(114)* Topical therapy, among other non-systemic treatments, are associated with low rates of AEs.

The 2023 article by ***Elsayed et al.*** "Treatment Options of Onychomycosis: Review Article" from the Zagazig University from **Egypt** emphasises that topical antifungals are effective only in combination with nail debridement and that **oral therapy** is limited by medication interactions and possible **hepatotoxicity**. **Combinations** of systemic and topical **treatments** seem to be the **most successful** treatment. Authors consider **ciclopirox 8%** lacquer to be an **effective topical agent** against wide range of microorganisms, including Gram-positive and -negative bacteria, dermatophytes, *Candida*, and even some non-dermatophytic fungus. *(116)*

The 2022 review article by ***Gupta et al.*** "Onychomycosis in Older Adults: Prevalence, Diagnosis, and Management" includes **ciclopirox 8% lacquer** as part of the topical treatment options for onychomycosis in older adults, recommended for mild (≤ 25% nail involvement) to moderate (26–74%) onychomycosis without nail matrix involvement. It also suggests that **combinations** of oral therapy and other measures such as mechanical

debridement or topical antifungal (including ciclopirox 8% lacquer) could be beneficial when the nail is thick (> 3 mm), exhibits extensive and lateral onycholysis or longitudinal streaks, or is a dermatophytoma. *(52)*

The 2021 review article by ***Gupta et al.*** "A Paradigm Shift in the Treatment and Management of Onychomycosis" from **Canada** recommends **ciclopirox 8% lacquer** in Europe as topical therapy for **onychomycosis active treatment** and for **prophylaxis in the post-treatment phase** for patients that have achieved cure in the active treatment. For patients who fail therapy or show poor response to initial monotherapy, oral terbinafine and itraconazole may be combined off-label with topical treatment, including ciclopirox 8% lacquer, as an alternative to combination therapy with terbinafine + itraconazole. *(118)*

The 2020 review article by ***Vikas et al.*** "Mechanistic Insights of Formulation Approaches for the Treatment of Nail Infection: Conventional and Novel Drug Delivery Approaches" from the **Charotar University of Science & Technology of India** considers **ciclopirox** to be the **most** popular drug molecule for the **topical treatment of onychomycosis**, although it recognizes the **difficulties topical treatments** for onychomycosis face, mainly as penetration up to all infected sites of these deep-seated infections. The water-soluble film **HPCH**, found in ciclopirox 8% hydrolacquer, is notable for its strong film adhesion, due to its ability to form hydrogen bonds with keratin and hydrate the nail plate for optimal adhesion. This enhanced adhesion improves drug permeation through the nail. *(120)*

The 2019 review article by ***Gupta et al.*** "Emerging drugs for the treatment of onychomycosis" from the dermatology research and clinical trials centre Mediprobe Research Inc. (**Canada**) includes **ciclopirox 8% hydrolacquer with HPCH** as part of the **topical penetration enhancers** for onychomycosis treatment, considering that the **novel formulation** was **more active** and **better tolerated** than the currently available ciclopirox lacquer. Experts considered **topical drug delivery** to the nail is an attractive alternative to systemic therapies for onychomycosis due to the **fewer risks of drug-drug interactions and systemic events**, which may result in greater patient compliance, although reported mycological cure rates were considered relatively low for topical treatments. *(121)*

The 2019 article by ***Lindblad et al.*** "Putting the fun in fungi: toenail onychomycosis" from the Alberta College of Family Physicians and the Department of Family Medicine at the University of Alberta **(Canada)** recommends saving topical treatment for cases with minimal (≤ 20% to 40%) nail involvement and mentions topical ciclopirox efficacy evidence. *(122)*

The 2019 article by ***Gupta et al. "***Global perspectives for the management of onychomycosis" from the dermatology research and clinical trials centre Mediprobe Research Inc. (**Canada**) conducted a study surveying experts from Canada, the United States, Italy, the United Kingdom, Israel, India, and Brazil. Most surveyed experts used systemic, topical, and combination treatments approved in their countries. **Ciclopirox was used by experts to treat mild and moderate onychomycosis in the US, Canada and Europe.** It was also used

to treat mild onychomycosis in **South America**. Besides that, several of the experts preferred to prescribe topical treatments, including ciclopirox lacquer, in children, diabetic individuals, and mixed infections. Experts considered that patients with hepatic dysfunction and hepatitis could benefit form topical treatment because oral treatment for onychomycosis can be associated with hepatotoxicity. Patients with diabetes could also benefit from topical treatment as it encourages regular inspection of the foot. When appropriate, topical treatments can be paired with other therapies, such as oral antifungals or devices, to potentially increase cure rates. *(53)*

The 2014 article by ***Gupta et al.*** "Management of Onychomycosis in **Canada** in 2014" from the University of Toronto included **ciclopirox 8% lacquer** as part of the onychomycosis treatments options available. Recommendations included: 1) oral terbinafine with or without topical treatment (ciclopirox or efinaconazole lacquers) for dermatophyte onychomycosis; 2) topical treatment for non-dermatophyte moulds (NDMs) milder cases; 3) terbinafine with or without topical treatment for mixed dermatophyte/NDM infections; and 4) oral treatment combined with efinaconazole lacquer for onychomycosis caused by *Candida*. *(126)*

The 2003 article by ***Ballesté et al.*** "Onychomycosis. A review of the topic" from the **Clinic Hospital – University of the Republic (Uruguay)** highlights the importance of having the active substance associated with an **adequate vehicle** for onychomycosis treatment, like a lacquer, as otherwise there will not be adequate nail diffusion. Lacquers ensure that the active ingredient remains in contact with the nail for a prolonged period, allowing for slow, sustained drug release at appropriate concentrations. **Ciclopirox olamine 8%** is an antifungal agent with activity against dermatophytes, yeasts, and other filamentous fungi (dematiaceous and hyaline). *(127)*

The patient guide "Your Complete Guide to Toenail Fungal Infections" by the **Canadian Skin Patient Alliance** included **ciclopirox 8%** lacquer as one of the available treatment options, for mild to moderate nail fungus along with a treatment program that includes regular removal of the infected nail. *(128)*

9.4. Recommendations for Systemic Treatment

Other associations and entities only recommend systemic treatment for onychomycosis (Table 8). The **National Department of Health** from **South Africa** recommends oral fluconazole. *(129)* The **Mexican Institute of Social Security** recommends oral treatment with terbinafine, itraconazole or fluconazole for dermatophyte fungus and itraconazole, and terbinafine or fluconazole for yeast-caused onychomycosis. *(130)* The "Standard Treatment Guidelines and National Essential Medicines List for Tanzania Mainland" from the **Ministry of Health os T**, Community Development, Gender, Elderly and Children from **Tanzania** recommends oral treatment with fluconazole, terbinafine and itraconazole. *(131)* The **PAHO** recommends oral treatment with terbinafine (first choice) or itraconazole. *(102)*

Table 8. National and International Guidelines and Articles that Only Recommend Systemic Treatment for Onychomycosis

Author/Organization	Country/Region	Title	Publication date
Pan American Health Organization (PAHO) *(102)*	America	Infectious Diseases Treatment 2024-2026. Ninth Edition	2024
Ministry of Health, Community Development, Gender, Elderly and Children *(131)*	Tanzania	Standard Treatment Guidelines and National Essential Medicines List for Tanzania Mainland	2023
National Department of Health *(129)*	South Africa	Standard Treatment Guidelines and Essential Medicines List for South Africa. Hospital Level, adults.	2019
Mexican Institute of Social Security In *(130)*	Mexico	Clinical Practice Guideline, Diagnosis and Treatment of Tinea and Onychomycosis at the Primary Care Level. Mexico: Mexican Institute of Social Security	2009

Acronyms: PAHO: Pan American Health Organization.

10. Summary of Available Data on Comparative Cost and Cost-Effectiveness

A literature review was conducted across biomedical databases to retrieve all relevant evidence on ciclopirox cost and cost-effectiveness. The search was complemented with hand searches in the grey literature, including the webpages from the Ministry of Health and Medicines and Health Technology Assessment agencies of multiple countries, and additional databases. The inclusion and exclusion criteria, search terms and PRISMA flow diagram are presented in Appendix I: Literature Review search terms and PRISMA flow diagrams

No studies evaluating the cost or cost-effectiveness of ciclopirox 8% HPCH hydrolacquer were identified. Therefore, we present the evidence found for ciclopirox 8% water insoluble lacquer.

Twelve studies that included ciclopirox 8% water insoluble lacquer were retrieved. Eight studies had positive results for ciclopirox lacquer cost-effectiveness or costs when compared to **oral terbinafine, itraconazole, fluconazole** and **griseofulvin**, and **topical amorolfine, efinaconazole, tavaborole** and **tioconazole**, *(132-139)* one study had positive results for amorolfine 5% lacquer when compared to ciclopirox 8% water insoluble lacquer, *(140)* one

study had positive results for oral terbinafine when compared to oral itraconazole and topical ciclopirox 8% water insoluble lacquer, *(141)* one study considered amorolfine 5% nail lacquer to be more cost-effective than ciclopirox 8% water insoluble lacquer and tioconazole 28% for onychomycosis of toenail, *(142)* and one study concluded that terbinafine oral treatment (pulse, continuous, or in combination with other agents) was the most cost-effective treatment option when compared to oral itraconazole, griseofulvin, and fluconazole and topical ciclopirox water insoluble lacquer. *(143)* The main studies are sumarised below.

The study by ***Roster et al.*** (2024) *(132)* and the study ***by Wang et al.*** (2022) *(133)* concluded that **ciclopirox was the most prescribed topical treatment** within the Medicare setting in the US (compared to topical **efinaconazole and tavaborole**)**.** Additionally, results showed that physicians had a stronger consideration for price when selecting both topical and systemic treatments, with the least expensive medications (topical ciclopirox and systemic terbinafine) accounting for nearly 98% of all prescriptions. *(132)*

The study by ***Paul et al.*** (2013), conducted in France and Tunisia, concluded that the sequential (SEQ) treatment involving urea-based ointment, nail debridement, ciclopirox olamine 1% cream, and ciclopirox 8% film-forming solution resulted in a higher complete cure rate and lower treatment cost (50% lower) per complete cured patient for toenail onychomycosis compared to amorolfine 5% nail lacquer alone. Thus, **the SEQ treatment involving ciclopirox 8% lacquer demonstrated greater efficacy and a better cost-effectiveness profile compared to amorolfine 5% lacquer.** *(135)*

The study by ***Gupta et al.*** (2006) concluded that **ciclopirox water insoluble lacquer is a cost-effective** antifungal treatment within the Canadian healthcare system, owing to its lower drug acquisition costs compared to **continuous terbinafine and pulse itraconazole.** *(138)*

The study by ***Ribera Pibernat et al.*** (2005) concluded that **topical treatment with ciclopirox 8% water insoluble nail lacquer** was the **most efficient therapeutic alternative** when compared to **amorolfine and tioconazole nail lacquers** for treating patients with superficial white onychomycosis and/or mild distal onychomycosis in the Spanish setting. *(139)*

The study by ***Gupta et al.*** (2002) concluded that **ciclopirox 8% water insoluble lacquer** demonstrated the **lowest regimen costs, lowest cost per mycologic cure, and the lowest cost per expected disease-free day** and that it can be considered a cost-effective option for the management of dermatophyte toenail onychomycosis in the US context when compared to oral terbinafine, itraconazole (pulse), and fluconazole, and dominating (associated with better health results and lower costs) when compared to oral griseofulvin and itrazonazole continuous treatment. *(136)*

Finally, the study ***Gupta et al.*** (2000) concluded that Ciclopirox water insoluble nail lacquer had the lowest drug acquisition cost of all comparators, lowest cost per mycologic cure, lowest cost of medical management and lowest cost of regimen in the US. Treatment with **ciclopirox lacquer can be considered a cost-effective option when compared to oral itraconazole (pulse), terbinafine, and fluconazole, and dominating when compared to oral griseofulvin and itraconazole (continuous treatment),** meaning it was associated with lower costs and better health results. *(137)*

The main study details are described in Appendix III: Description of the main cost and cost-effectiveness studies

Sponsorship

All studies were sponsored, **except** for:

1) The study ***by Roster et al.*** *(132)* which concluded that topical ciclopirox and systemic terbinafine where being prescribed most often for onychomycosis, probably due to their lower price, showing that physicians had a strong consideration for price when selecting treatments.
2) The study by ***Wang et al.*** *(133)* which concluded that ciclopirox 8% lacquer was the most commonly prescribed topical treatment in the US, likely due to factors like easy accessibility, generics availability, low cost, and strong safety and efficacy profiles.
3) The study by ***Singh et al.*** *(134)* which concluded that ciclopirox (cream and lacquer) and terbinafine (cream) were prescribed most frequently by all provider types (likely attributable to payers and clinicians being more comfortable with using older, more established drugs), and that expenditure grew at a slower rate than utilization for terbinafine (0.3:1) and Ciclopirox (0.4:1) (as opposed to efinaconazole (1.3:1) and tavaborole (1.3:1).
4) The study by ***Warshaw et al.*** *(143)* which compared oral terbinafine, itraconazole, griseofulvin, and fluconazole; and topical ciclopirox.

10.1. Prices for Ciclopirox 8% HPCH hydrolacquer

The public prices of ciclopirox 8% HPCH hydrolacquer in a selection of key markets according to availability (see section 11), are shown in

Table 9. In 20 out of 39 markets where ciclopirox 8% HPCH is available, prices are accessible at public domain.

Similarly, comparative public prices for all nail lacquers (e.g., ciclopirox – either water soluble formulations or not –, amorolfine, terbinafine, efinaconazole and tavaborole) in those countries where price for ciclopirox 8% HPCH is available are shown in

Table 10. Both **efinaconazole and tavaborole are not available in all of the analyzed markets** except for Argentina (e.g., only efinaconazole), where its price is similar to ciclopirox 8% HPCH. In general, efinaconazole has been potentially identified only in 5 countries worldwide (e.g., Argentina, Canada, Egypt, Japan and United States) whereas tavaborole might only be available in Egypt and United States.

In 17 out of the 20 countries analyzed, ciclopirox is the cheapest option (dominant) among the antifungal lacquers available in each market (e.g., Argentina, Belgium, Bulgaria, Chile, Denmark, France, Greece, Lebanon, Lithuania, Norway, Peru, Poland, Portugal, Slovakia, Spain, Sweden and Switzerland). Out of the 17 countries were ciclopirox was dominant, **in 11 it was due to ciclopirox 8% HPCH formulation**.

In 14 out of the 20 countries analyzed, the formulation of ciclopirox 8% HPCH is the only available or the cheapest among other ciclopirox formulations. In Spain, for instance, all ciclopirox lacquers have same price per mg, regardless of composition (e.g., HPCH, other excipients).

In case of ciclopirox, amorolfine and terbinafine formulations, generics or hybrids are already available in several markets.

Table 9. Prices for Ciclopirox 8% HPCH available in the public domain

Country	Product Name	Strength	Price local currency	Price type	Source	Currency exchange rate (04/10/2024 - Oanda)	Price in USD ($)	Notes
Argentina	Niogermox	80 mg/g, 3.3 mL	ARS 27,059.65	PPI VAT	Link *(144)*	0.00103	$ 27.87	N/A
Australia	RejuveNail	80 mg/g, 3.3 mL and 6.6 mL	N/A	N/A	Link *(145)*	N/A	N/A	Not included in PBS
Austria	Kitonail	80 mg/g	Not public	N/A	N/A	N/A	N/A	N/A
Belgium	Myconail	80 mg/g, 6.6 mL	EUR 34.00	PPI VAT	Link *(146)*	1.10326	$ 37.51	N/A
Bolivia	Ony-tec	80 mg/g, 3.3 mL	Not public	N/A	N/A	N/A	N/A	N/A
Bulgaria	Polinail	80 mg/g, 3.3 mL and 6.6 mL	BGN 53.33 (3 mL) BGN 66.94 (6.6 mL)	Max. selling price	Link *(147)*	0.56409	$ 30.08 (3.3 mL) $ 37.76 (6.6 mL)	N/A
Chile	Privex	80 mg/g, 3.3 mL	CLP 22,884.00	MNF/PPP	Link *(148)*	0.00109	$ 24.94	N/A
Colombia	Niogermox	80 mg/g	Not public	N/A	N/A	N/A	N/A	N/A
Cyprus	Kitonail	80 mg/g, 3.3 mL and 6.6 mL	N/A	N/A	Link *(149)*	N/A	N/A	Price not published
Czech Republic	Polinail	80 mg/g, 3.3 mL	CZK 515.39	Max. pharmacy price	Link *(13)*	0.043553	$ 22.45	N/A

Country	Product Name	Strength	Price local currency	Price type	Source	Currency exchange rate (04/10/2024 - Oanda)	Price in USD ($)	Notes
Denmark	Onytec	80 mg/g, 6.6 mL	DKK 152.00	PPP	Link *(150)*	0.1479	$ 22.48	N/A
Ecuador	Ony-tec	80 mg/g, 3.3 mL and 6.6 mL	Not public	N/A	N/A	N/A	N/A	N/A
Finland	Onytec	80 mg/g, 6.6 mL	EUR 43.24	PPI VAT	Link *(151)*	1.10326	$ 47.40	N/A
France	Onytec	80 mg/g, 3.3 mL and 6.6 mL	EUR 8.56 (3.3 mL) EUR 14.89 (6.6 mL)	PPI VAT	Link *(152)*	1.10326	$ 9.44 (3.3 mL) $ 16.42 (6.6 mL)	N/A
Germany	Ciclopoli	80 mg/g, 3.3 mL and 6.6 mL	Not public	N/A	N/A	N/A	N/A	N/A
Greece	Kitonail	80 mg/g, 6.6 mL	EUR 11.94	PPI VAT	Link *(19)*	1.10326	$ 13.17	N/A
Hungary	Kitonail	80 mg/g, 3.3 mL and 6.6 mL	N/A	N/A	N/A	N/A	N/A	Not included in NEAK
Ireland	Onytec	80 mg/g	N/A	N/A	N/A	N/A	N/A	Not marketed
Israel	Ciclopoli	80 mg/g	Not public	N/A	N/A	N/A	N/A	N/A
Italy	Niogermox	80 mg/g, 3.3 mL and 6.6 mL	Not Public	N/A	N/A	N/A	N/A	N/A
(South) Korea	Fulcare	80 mg/g, 3.3 mL and 6.6 mL	Not public	N/A	N/A	N/A	N/A	N/A

Country	Product Name	Strength	Price local currency	Price type	Source	Currency exchange rate (04/10/2024 - Oanda)	Price in USD ($)	Notes
Latvia	Onytec	80 mg/g, 3.3 mL	EUR 29.95	PPI VAT	Link *(26)*	1.10326	$ 33.04	N/A
Lebanon	Onytec	80 mg/g, 6.6 mL	LL 2,129,990.33	PPI VAT	Link *(27)*	0.00001	$ 21.30	N/A
Lithuania	Onytec	80 mg/g, 3.3 mL and 6.6 mL	EUR 27.63* (3.3 mL) EUR 43.83 (6.6 mL)	PPI VAT	Link *(153)*	1.10326	$ 30.49 (3.3 mL) $ 48.36 (6.6 mL)	N/A
Mexico	Niogermox	80 mg/g	N/A	N/A	Link *(154)*	N/A	N/A	N/A
New Zealand	Rejuvenail	80 mg/g, 3.3 mL and 6.6 mL	N/A	N/A	Link *(155)*	N/A	N/A	Not included in PHARMAC
Norway	Onytec	80 mg/g, 6.6 mL	NOK 229.50	PPI VAT	Link *(31)*	0.09427	$ 21.63	N/A
Peru	Ony-tec	80 mg/g, 3.3 mL	PEN 142.51	PPP	Link *(156)*	0.26747	$ 32.12	N/A
Poland	Polinail	80 mg/g, 3.3 mL	PLN 70	PPI VAT	Link *(157)*	0.25635	$ 17.94	N/A
Portugal	Niogermos	80 mg/g, 6.6 mL	EUR 17.49	PPI VAT	Link *(158)*	1.10326	$ 19.30	N/A
Romania	Kitonail	80 mg/g	Not public	N/A	N/A	N/A	N/A	N/A
Russia	Ciclopoli	80 mg/g	Not public	N/A	N/A	N/A	N/A	N/A
Slovakia	Polinail	80 mg/g, 3.3 mL	EUR 10.18	MNF	Link *(159)*	1.10326	$ 11.23	N/A

Country	Product Name	Strength	Price local currency	Price type	Source	Currency exchange rate (04/10/2024 - Oanda)	Price in USD ($)	Notes
Slovenia	Onytec	80 mg/g	N/A	N/A	Link *(160)*	N/A	N/A	Not included in JAZMP
Spain	Ony-tec	80 mg/g, 6.6 mL	EUR 16.59	PPI VAT	Link *(161)*	1.10326	$ 18.30	N/A
Sweden	Onytec	80 mg/g, 6.6 mL	SEK 366.50	PPI VAT	Link *(162)*	0.09708	$ 35.58	N/A
Switzerland	Ciclopoli	80 mg/g, 3.3 mL and 6.6 mL	CHF 30.15 (3.3 mL) CHF 38.75 (6.6 mL)	PPI VAT	Link *(41)*	1.1742	$ 35.40 (3.3 mL) $ 45.50 (6.6 mL)	N/A
United Kingdom	Onytec	80 mg/g	N/A	N/A	N/A	N/A	N/A	Not included in the NHS
Venezuela	Onytec	80 mg/g, 3.3 mL and 6.6 mL	N/A	N/A	N/A	N/A	N/A	No national prices available

Notes: *Average price from 2 different manufacturers. | Acronyms: ARS: Argentine Peso; BGN: Bulgarian Lev; CHF: Swiss Franc; CLP: Chilean Peso; CZK: Czeh Koruna; DKK: Danish Krone; EUR: Euro; JAZMP: Agency for Medicinal Products and Medical Devices of the Republic of Slovenia; LL: Lebanese Lira; MNF: Manufacturer Price; N/A: Not Available; NEAK: National Health Insurance Fund; NHS: National Health Service; NOK: Norwegian Krone; PBS: Pharmaceutical Benefits Scheme; PEN: Peruvian Nuevo Sol; PHARMAC: Pharmaceutical Management Agency; PLN: Zloty; PPI: Public Price; PPP: Pharmacy Purchase Price; SEK: Swedish Krona; VAT: Value-Added Tax.

Table 10. Prices for nail lacquers indicated for onychomycosis in different countries available in the public domain, adjusted as PPI VAT

Country	Ciclopirox Price in USD ($)**	Ciclopirox 8% HPCH Price in USD ($)	Amorolfine Price in USD ($)	Terbinafine Price in USD ($)	Efinaconazole Price in USD ($)	Tavaborole Price in USD ($)	Price type	Source
Argentina	**$ 11.52*** (8%, 5 mL)†	**$ 27.87** Niogermox 80 mg/g, 3.3 mL)	**$ 50.10** (Laquifun 5%, 4 mL) **$ 35.53*** (5%, 5 mL)†	N/A	**$ 32.17*** (10%, 4 mL)	N/A	PPI VAT	Link *(144)*
Belgium	**$ 23.40** (Mycoster 8%, 3 mL)	**$ 37.51** (Myconail 8%, 6.6 mL)	**$ 43.02*** (5%, 5 mL)†	N/A	N/A	N/A	PPI VAT	Link *(146)*
Bulgaria	**$ 36.60** (Batrafen 8%, 3 g)	**$ 30.08** (Polinail 8%, 3.3 mL)	**$ 26.04** (Fungiter 5%, 2.5 mL)†	**$ 33.85** (Exoterbyn 7.82%, 3.3 mL)	N/A	N/A	Max. selling price	Link *(147)*
Chile	**$ 19.67*** (8%, 5 mL)†	**$ 31.17** (Privex, 80 mg/g, 3.3 mL)	**$ 18.95** (Micolac 5%, 3 mL)	N/A	N/A	N/A	PPI VAT‡	Link *(148)*
Czech Republic	N/A	**$ 22.45** (Polinail 8%, 3.3 mL)	**$ 25.39** (Amorolfine Belupo 5%, 5 mL)†	N/A	N/A	N/A	Max. pharmacy price	Link *(13)*
Denmark	N/A	**$ 30.91** (Onytec 8%, 6.6 mL)	N/A	N/A	N/A	N/A	PPI VAT‡	Link *(150)*
Finland	N/A	**$ 47.40** (Onytec 8%, 6.6 mL)	**$ 28.32*** (5%, 5 mL)†	N/A	N/A	N/A	PPI VAT	Link *(151)*
France	**$ 7.44*** (8%, 3 mL)†	**$ 9.44** (Onytec 80 mg/g, 3.3 mL)	**$ 11.45*** (5%, 2.5 mL)†	N/A	N/A	N/A	PPI VAT	Link *(152)*

Country	Ciclopirox Price in USD ($)**	Ciclopirox 8% HPCH Price in USD ($)	Amorolfine Price in USD ($)	Terbinafine Price in USD ($)	Efinaconazole Price in USD ($)	Tavaborole Price in USD ($)	Price type	Source
Greece	**$ 10.78** (Mycomycen 8%, 6 mL)	**$ 13.17** (Kitonail 80 mg/g, 6.6 mL)	**$ 20.07*** (5%, 5 mL)†	N/A	N/A	N/A	PPI VAT	Link *(19)*
Latvia	N/A	**$ 33.04** (Onytec 8%, 3.3 mL)	**$ 38.64*** (5%, 2.5 mL)†	**$ 31.98** (Exotafin 7.82%, 3.3 mL)	N/A	N/A	PPI VAT	Link *(26)*
Lebanon	**$ 7.57** (Mycoster 8%, 3 mL)	**$ 21.30** (Onytec 8%, 6.6 mL)	**$ 9.15*** (5%, 2.5 mL)	N/A	N/A	N/A	PPI VAT	Link *(27)*
Lithuania	N/A	**$ 30.49** (Onytec 8%, 3.3 mL)	**$ 31.35*** (5%, 2.5 mL)†	**$ 31.11*** (7.82%, 3.3 mL)†	N/A	N/A	PPI VAT	Link *(153)*
Norway	N/A	**$ 21.63** (Onytec 8%, 6.6 mL)	**$ 16.59** (Loceryl 5%, 5 mL)	N/A	N/A	N/A	PPI VAT	Link *(31)*
Peru	**$ 93.74** (Micopirox 8%, 5 mL)	**$ 50.70** (Ony-tec 8%, 3.3 mL)	**$ 87.05** (Loceryl 5%, 2.5 mL)	N/A	N/A	N/A	PPI VAT‡	Link *(156)*
Poland	**$ 16.48** (Pirolam 8%, 4 g)†	**$ 17.94** (Polinail 80 mg/g, 3.3 mL)	**$ 15.58*** (5%, 5 mL) †	N/A	N/A	N/A	PPI VAT	Link *(157)*
Portugal	**$ 9.77** (Mycoster 8%, 3 mL)	**$ 19.30** (Niogermos 8%, 6.6 mL)	N/A	N/A	N/A	N/A	PPI VAT	Link *(158)*

Country	Ciclopirox Price in USD ($)**	Ciclopirox 8% HPCH Price in USD ($)	Amorolfine Price in USD ($)	Terbinafine Price in USD ($)	Efinaconazole Price in USD ($)	Tavaborole Price in USD ($)	Price type	Source
Slovakia	N/A	**$ 16.38** (Polinail 8%, 3.3 mL)	**$ 43.94** (Loceryl 5%, 5 mL)	N/A	N/A	N/A	PPI VAT‡	Link *(159)*
Spain	**$ 18.30*** (8%, 6.6 mL)†	**$ 18.30** (Onytec 8%, 6.6 mL)	**$ 23.64*** (5%, 5 mL)†	N/A	N/A	N/A	PPI VAT	Link *(161)*
Sweden	N/A	**$ 35.58** (Onytec 8%, 6.6 mL)	**$ 24.33*** (5%, 3 mL)†	**$ 34.85** (Terclara 98 mg/mL, 5 mL)	N/A	N/A	PPI VAT	Link *(162)*
Switzerland	**$47.73** (Ciclocutan 8%, 6.6 mL)	**$ 45.50** (Ciclopoli 8%, 6.6 mL)	**$ 41.39*** (5%, 5 mL)†	N/A	N/A	N/A	PPI VAT	Link *(41)*

Notes: Shaded light blue cells at country name indicate that Ciclopirox 8% HPCH is the only formulation available in those countries or the cheapest among other Ciclopirox formulations; Shaded cells in grey indicate the cheapest option among all the antifungal lacquers available in each market (e.g., dominant option); *Average price from different manufacturers; **Excluding Ciclopirox 8% HPCH; †Either hybrid, generics or parallel exports; ‡Calculated, from listed price at public domain to PPI VAT. | Acronyms: HPCH: Hydroxypropyl Chitosan; MNF: Manufacturer Price; N/A: Not Available; PPI: Public Price; PPP: Pharmacy Purchase Price; VAT: Value-Added Tax.

11. Regulatory Status, Market Availability and Pharmacopeial Standards

11.1. Regulatory Status and Market Availability of Ciclopirox

The regulatory status and market availability of the ciclopirox 8% HPCH hydrolacquer in 39 markets is shown in Table 11.

In general, ciclopirox without HPCH excipient is available in 33 countries worldwide, and **in 19 out of these 33, ciclopirox 8% HPCH is also available** (see in *italics* Ciclopirox 8% + HPCH): Algeria, *Argentina*, *Austria*, Azerbaijan, *Belgium*, Brazil, *Bulgaria*, Canada, *Chile*, *Colombia*, Croatia, Egypt, *France*, *Germany*, *Greece*, *Hungary*, India, *Italy*, *Lebanon*, *Mexico*, Nicaragua, Paraguay, *Peru*, *Poland*, *Portugal*, *South Korea, Spain*, *Switzerland*, Tunisia, Turkey, United States, Uruguay, and Vietnam.

There are **20 countries** additional in the world where the **only ciclopirox formulation available is 8% HPCH** (i.e., Australia, Bolivia, Cyprus, Czech Republic, Denmark, Ecuador, Finland, Ireland, Israel, Latvia, Lithuania, New Zealand, Norway, Romania, Russia, Slovakia, Slovenia, Sweden, United Kingdom and Venezuela).

Table 11. Regulatory status of Ciclopirox 8% HPCH worldwide

Country	Product Description	Marketing Authorization Status	Registration Year	Marketing Status	Source
Argentina	Niogermox	Approved	N/A	Marketed	ANMAT *(2)*
Australia	RejuveNail Anti-fungal Nail Lacquer	Approved	2012	Marketed	TGA *(3)*
Austria	Kitonail 80 mg/g medicated nail polish	Approved	2009	Marketed	BASG *(4)*
Belgium	Myconail 80 mg/g medic. nail lacquer	Approved	2012	Marketed	FAMHP *(5)*
Bolivia	Ony-tec	Approved	2023	Marketed	AGEMED *(6)*
Bulgaria	Polinail 80 mg/g medicated nail polish	Approved	N/A	Marketed	BDA *(163)*
Chile	Privex Topical Nail Lacquer Solution 8%	Approved	2009	Marketed	ISPCH *(10)*
Colombia	Niogermox	Approved	2017	Marketed	INVIMA *(164)*

Country	Product Description	Marketing Authorization Status	Registration Year	Marketing Status	Source
Cyprus	Kitonail Medicated Nail Lacquer 80 mg/g	Approved	2012	Marketed	PHS *(12)*
Czech Republic	Polinail	Approved	2009	Marketed	SÚKL *(13)*
Denmark	Onytec	Approved	2012	Marketed	DKMA *(14)*
Ecuador	Ony-tec 8% Topical Nail Lacquer Solution	Approved	2011	Marketed	ARCSA *(165)*
Finland	Onytec	Approved	2012	Marketed	Fimea *(16)*
France	Onytec 80 mg/g Medicated Nail Lacquer	Approved	2009	Marketed	ANSM *(17)*
Germany	Ciclopoli against onychomicosis	Approved	2008	Marketed	BfArM *(18)*
Greece	Kitonail Medicated Nail Lacquer 80 mg/g	Approved	2009	Marketed	EOF *(19)*
Hungary	Kitonail Medicated Nail Lacquer 80 mg/g	Approved	2009	Marketed	OGYÉI *(20)*
Ireland	Onytec 80 mg/g Medicated Nail Lacquer	Approved	2012	Not Marketed	HPRA *(21)*
Israel	Ciclopoli 8% (80 mg/g)	Approved	N/A	Marketed	Israel Ministry of Health - Pharmaceutical Division *(22)*
Italy	Niogermox 80 mg/g Medicated Nail Polish	Approved	2010	Marketed	AIFA *(24)*
(South) Korea	Fulcare Nail Lacquer	Approved	2008	Marketed	MFDS *(25)*
Latvia	Onytec	Approved	2012	Marketed	ZVA *(26)*
Lebanon	Onytec	Approved	2012	Marketed	MOPH *(27)*
Lithuania	Onytec	Approved	2012	Marketed	VVKT *(28)*
Mexico	Niogermox	Approved	2015	Marketed	COFEPRIS *(166)*
New Zealand	Rejuvenail	Approved	2010	Marketed	MEDSAFE *(30)*

Country	Product Description	Marketing Authorization Status	Registration Year	Marketing Status	Source
Norway	Onytec	Approved	2013	Marketed	NOMA *(31)*
Peru	Ony-tec 8%	Approved	N/A	Marketed	DIGEMID *(167)*
Poland	Polinail	Approved	2009	Marketed	URPL *(33)*
Portugal	Niogermos	Approved	2009	Marketed	Infarmed *(34)*
Romania	Kitonail 80 mg/g	Approved	2009	Marketed	NAMMDR *(35)*
Russia	Ciclopoli 8%	Approved	N/A	Marketed	Roszdravnadzor *(36)*
Slovakia	Polinail	Approved	2009	Marketed	ŠÚKL *(37)*
Slovenia	Onytec 80 mg/g Medicated Nail Lacquer	Approved	2013	Marketed	JAZMP *(38)*
Spain	Ony-tec 80 mg/g Medicated Nail Lacquer	Approved	2010	Marketed	AEMPS *(39)*
Sweden	Onytec	Approved	N/A	Marketed	LV *(40)*
Switzerland	Ciclopoli Nail Lacquer	Approved	2009	Marketed	FOPH *(41)*
United Kingdom	Onytec 80 mg/g Medicated Nail Lacquer	Approved	N/A	Marketed	MHRA *(42)*
Venezuela	Onytec 8%	Approved	2012	Marketed	INHRR *(43)*

Acronyms: N/A: Not Available.

11.2. Pharmacopeial Standards

Availability of pharmacopeial standards for Ciclopirox:

- European Pharmacopoeia (Edition 11.0): *(168)*
  - Ciclopirox, 01/2017:1407
- US Pharmacopeia (USP 31st revision): *(169)*
  - Ciclopirox topical solution
  - Ciclopirox

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13. Appendix

13.1. Appendix I: Literature Review search terms and PRISMA flow diagrams

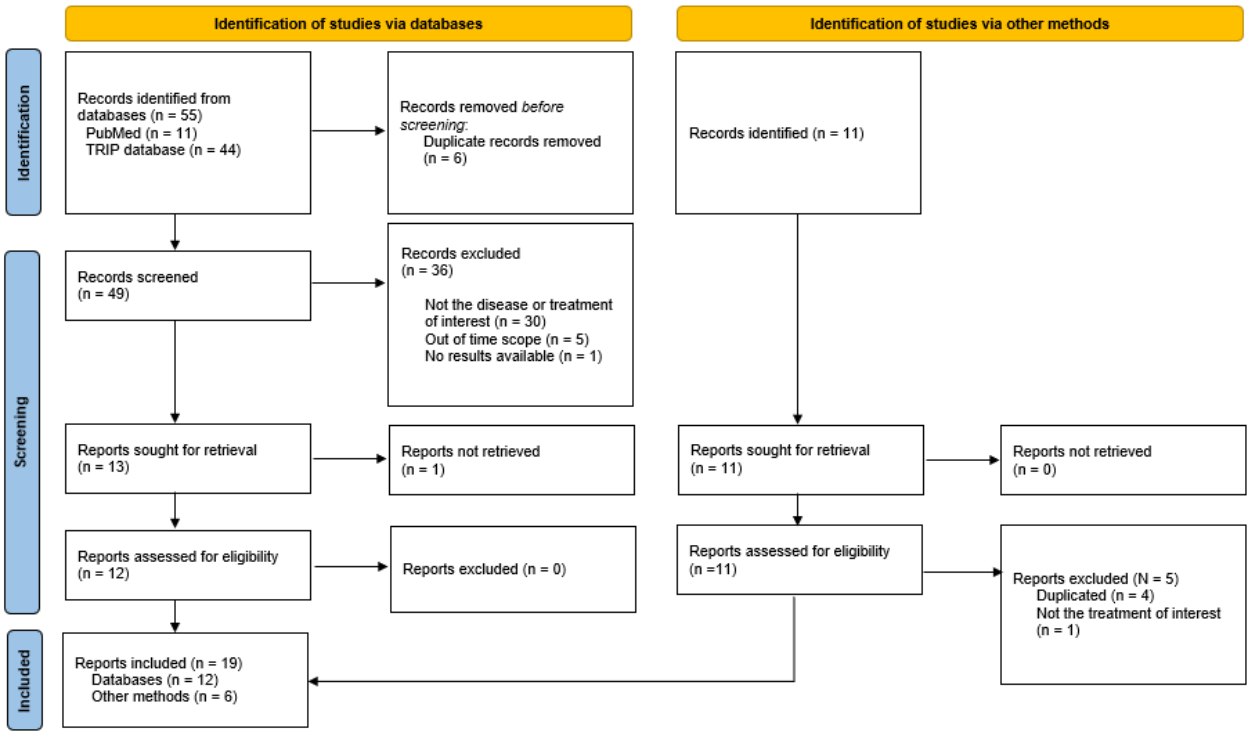
Supplementary Table 1. Literature Review search terms

CRITERIA	TRIP DATABASE SEARCH TERM
All criteria	Ciclopirox
CRITERIA	**PUBMED SEARCH TERM**
Clinical development program	((Ciclopirox[title]) OR (P-3051)) AND ((chitosan) OR (hydroxypropyl chitosan) OR (HPCH) OR (water-soluble) OR (hydrosoluble) OR (soluble)) AND ((trial[tiab]) OR (clinical[tiab]) OR (study[tiab]))
Guidelines	((onychomycosis[Title]) OR ("nail fungal infection"[Title]) OR ("fungal nail infection"[Title]) OR ("nail infection"[Title]) OR ("fungal infection"[Title])) AND ((guideline[Title]) OR ("clinical guideline"[Title]) OR (consensus[Title]) OR (management[Title]) OR ("treatment protocol"[Title]) OR ("treatment guidelines"[Title]) OR ("best practices"[Title]) OR (“treatment”[Title]) OR (“protocol”[Title]))
Cost and Cost-Effectiveness	((onychomycosis[Title]) OR (nail fungal infection[Title]) OR (fungal nail infection[Title]) OR (nail infection[Title]) OR (fungal infection[Title])) AND (economics[mesh])

Supplementary Table 2. Benefits and Harms Evidence Search Criteria

Inclusion criteria	Exclusion criteria
▪ Articles containing information on ciclopirox 8% HPCH hydrolacquer clinical development program (efficacy or safety) for onychomycosis treatment ▪ Language: english ▪ Geography: global	▪ Duplicated articles ▪ Articles not including ciclopirox in the analysis ▪ Articles published more than 25 years ago

Notes: No time restriction was applied in the TRIP Database search. | Acronyms: HPCH: Hydroxypropyl Chitosan.

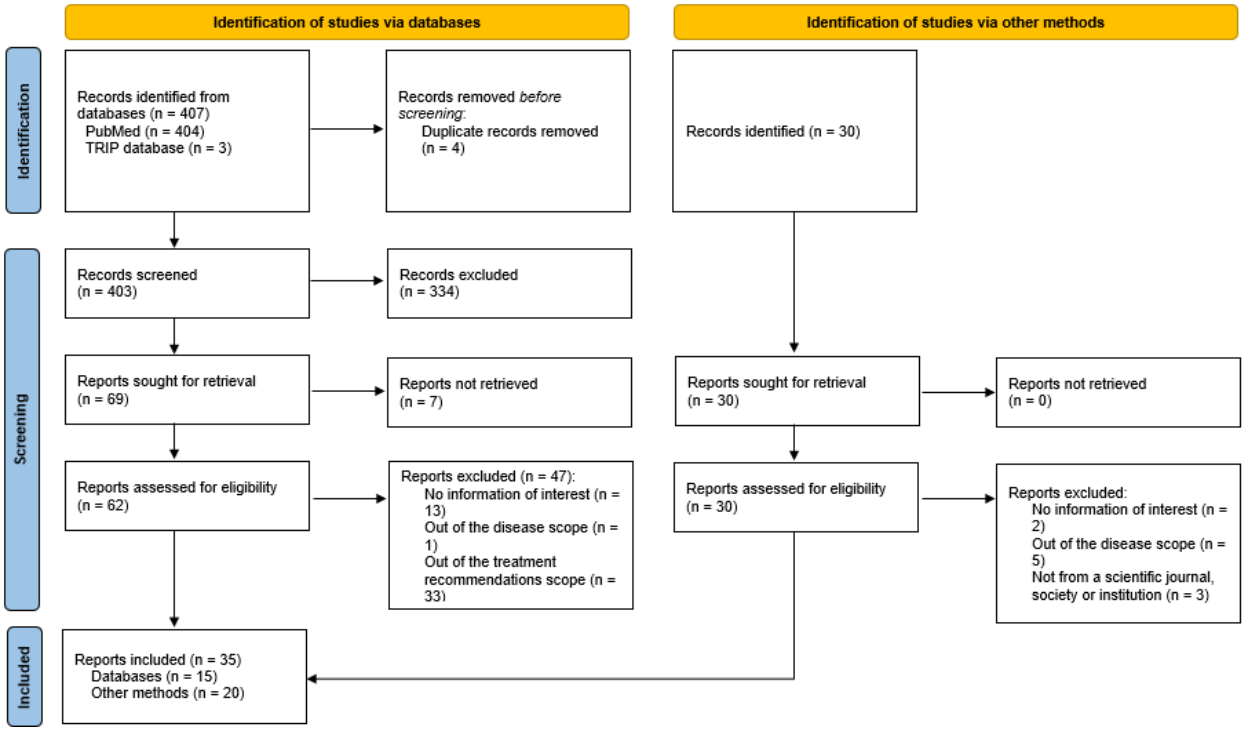


Supplementary Figure 1. *PRISMA flow diagram for the efficacy and safety literature review*

Supplementary Table 3. Clinical Guidelines Evidence Search Criteria

Inclusion criteria	Exclusion criteria
▪ Articles containing information on treatment recommendations for onycomycosis ▪ Language: english ▪ Geography: global	▪ Duplicated articles ▪ Articles published more than 25 years ago

Notes: no time restriction was applied in the TRIP Database search.

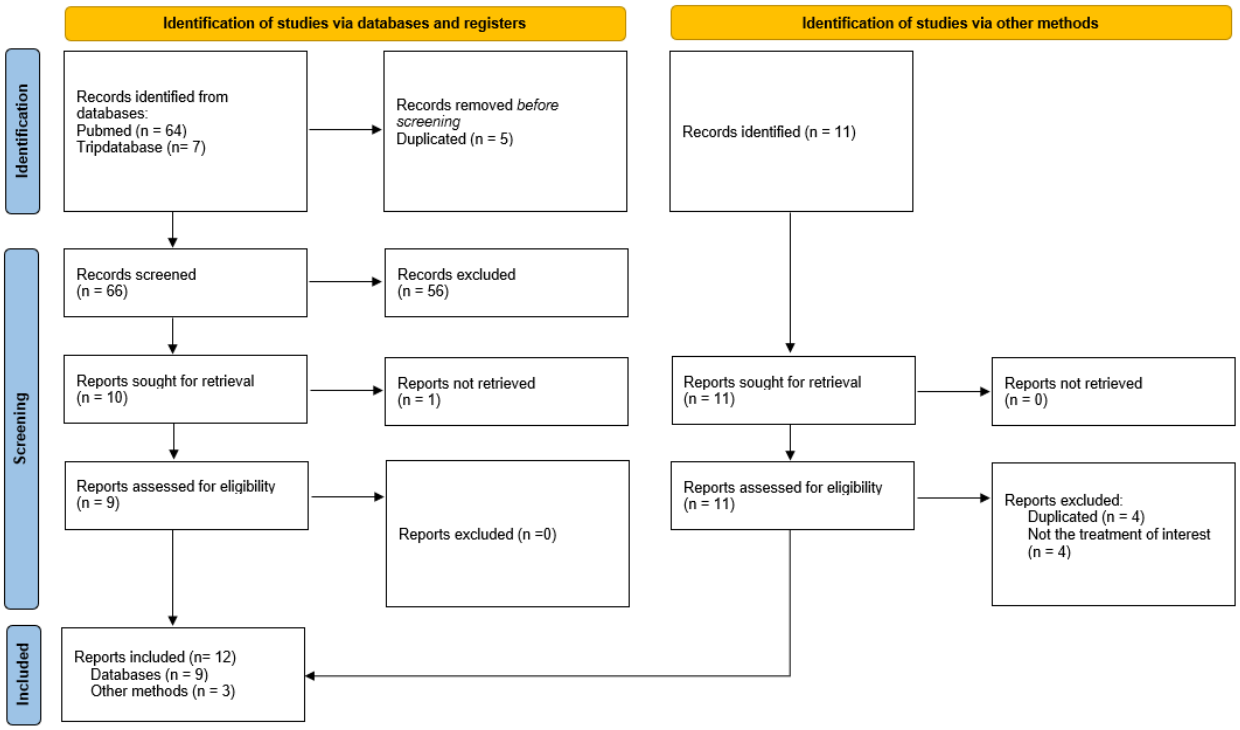


Supplementary Figure 2. PRISMA flow diagram for the clinical guidelines literature review

Supplementary Table 4. Cost and Cost-Effectiveness Evidence Search Criteria

Inclusion criteria	Exclusion criteria
▪ Articles containing information on costs, cost-effectiveness, or other relevant economic analyses related to ciclopirox lacquer for onychomycosis treatment ▪ Language: english ▪ Geography: global	▪ Duplicated articles ▪ Articles not including ciclopirox in the analysis ▪ Articles published more than 25 years ago

Notes: No time restriction was applied in the TRIP Database search.



Supplementary Figure 3. PRISMA flow diagram for the cost and cost-effectiveness literature review.

13.2. Appendix II: Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence and Grade of Recommendation

Supplementary Table 5. Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence.

Level of Evidence	Type of Study
I	Systematic reviews of RCT or individual RCT
II	Systematic reviews of cohort studies or individual cohort study
III	Systematic reviews of cohort studies, good quality case-control, or case-control study
IV	Case-series, poor-quality cohort, or case-control studies
V	Expert opinion

Acronyms: OCEBM: Oxford Centre for Evidence-Based Medicin; RCT: Randomized Clinical Trial | Source: (107)

Supplementary Table 6. Grade of Recommendation.

Grade	Level of Evidence
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies, or extrapolations from level 2 or 3 studies
D	Level 5 evidence or inconsistent studies at any level

Source: *(107)*

13.3. Appendix III: Description of the main cost and cost-effectiveness studies

1. A Retrospective Analysis of Prescribing Patterns of Onychomycosis Medications from 2016 to 2020 (2024)

a. Objective and Methodology

The objective of the ***Roster et al.*** "A Retrospective Analysis of Prescribing Patterns of Onychomycosis Medications from 2016 to 2020" study (2024) was to analyse the prescription pattern trends in the United States of topical treatment for onychomycosis (ciclopirox, efinaconazole, tavaborole) and oral medicines (terbinafine and itraconazole) from 2016 to 2020 stratified by generic and brand, costs, and healthcare specialty, using data from the Medicare Part D Prescribers database. *(132)* The study focused on prescribing trends among dermatologists, family and general practitioners, nurse practitioners, physician assistants, and podiatrists. The analysis examined the number of 30-day prescription claims for each

medication, associated prescription costs, and the proportion of branded versus generic medicines prescribed.

b. Results

The number of prescriptions increased by 9.4% each year from 2016 to 2019 and decreased by 7.7% from 2019 to 2020. Medicare expenditures for onychomycosis treatments increased by 4% in the studied period, with **topical ciclopirox and systemic terbinafine being prescribed most often**. **Physicians demonstrated a strong consideration for price** when selecting treatments, with the least expensive medications (ciclopirox and terbinafine) accounting for nearly 98% of all prescriptions. In contrast, the more costly medications (efinaconazole and tavaborole) were rarely prescribed.

Ciclopirox had a 6% annual growth change in 30-day claims and represented 65% of total antifungal prescription. It was also the most prescribed topical treatment.

c. Discussion

Cost consideration may partially explain why 90% and 91% of the time, the less expensive generic versions of ciclopirox and itraconazole, respectively, were prescribed. It also explains why the two most expensive medicines, efinaconazole ($807/30 days) and tavaborole ($1,131/30 days) represented only 1.5% of all antifungals prescribed in 2016 to 2020, despite efinaconazole demonstrating better efficacy than ciclopirox in clinical trials. Ciclopirox ($41/30 days) represented 65% of total antifungal prescriptions.

2. Analysis of utilization, cost and, prescription trends of onychomycosis medications among Medicare patients (2022)

a. Objective and Methodology

The objective of the ***Wang et al.*** "Analysis of utilization, cost and, prescription trends of onychomycosis medications among Medicare patients" study (2022) was to analyse onychomycosis antifungal prescription cost and trends in utilization by dermatologists in the United States. *(133)*

Medicare Part D data (2013-2018) was analysed for oral terbinafine and itraconazole, and topical ciclopirox, efinaconazole, and tavaborole prescribed by US dermatologists (other provider types were excluded). Supply days were determined by dividing the dispensed amount by the maximum daily usage, and total cost was calculated by multiplying the cost per supply day by the number of supply days.

b. Results

Regarding oral medications, terbinafine claims grew by an average of 6.7% annually from 2013 to 2018, while total spending increased by 15.1%. The growth outpaced spending due to a reduction in cost per supply day ($0.36 to $0.24). In comparison, itraconazole use was around 150 times less than terbinafine, peaking in 2014 and then declining by 0.9% annually.

Total spending on itraconazole decreased by 35.6%, with a 7.4% reduction in cost per supply day during the study period.

For topical antifungals, **ciclopirox claims grew by an average of 8.7% annually in the studied period, with total spending increasing by 66.9%. The rise in claims also outpaced spending due to a drop in cost per supply day ($2.50 to $1.70).** Efinaconazole claims peaked in 2015 but then declined by 5.6% annually, though both total cost and cost per supply day surged by 3091% and 144%, respectively, from 2014 to 2018. Tavaborole claims decreased by 0.9% annually between 2015 and 2018, with total spending down by 12.5%, but its cost per supply day increased by 42.4% annually over the same period.

Between 2013 and 2018, **dermatologist prescriptions for terbinafine and ciclopirox increased**, surpassing Medicare enrolment growth (14.3%). This was **likely due to factors like easy accessibility, generics availability, low cost, and strong safety and efficacy profiles. Ciclopirox was the most commonly prescribed topical treatment**, with 75% of the claims for topical treatments corresponding to ciclopirox and 25% to terbinafine. In contrast, itraconazole claims did not increase, likely due to its higher cost, frequent drug interactions, and less favourable safety profile. Despite no reported systemic side effects, efinaconazole and tavaborole claims remained flat, likely due to higher costs and lower accessibility compared to alternatives. Future prescribing trends may shift with patent expirations, new generics, and emerging treatments for onychomycosis.

c. Discussion

Ciclopirox was the most prescribed topical treatment for onychomycosis. As the most prevalent nail disease and with rising Medicare enrolment, onychomycosis treatment choices will significantly affect healthcare costs, therefore, factors such as the availability of generics and low cost, along with efficacy and safety, are likely to become key determinants in prescribing decisions.

3. A multicentre, randomized, open-label, controlled study comparing the efficacy, safety and cost-effectiveness of a sequential therapy with RV4104A ointment, Ciclopirox olamine cream and Ciclopirox film-forming solution with amorolfine nail lacquer alone in dermatophytic onychomycosis (2013)

a. Objective and Methodology

The objective of the ***Paul et al.*** "A multicentre, randomized, open-label, controlled study comparing the efficacy, safety and cost-effectiveness of a sequential therapy with RV4104A ointment, Ciclopirox olamine cream and Ciclopirox film-forming solution with amorolfine nail lacquer alone in dermatophytic onychomycosis" study (2013) was to compare the efficacy and safety of a sequential (SEQ) treatment with chemical nail avulsion and topical antifungals to amorolfine nail lacquer in dermatophytic onychomycosis. *(135)*

The study was a randomized (1:1), parallel-group, controlled study, comparing a 36-week SEQ treatment with chemical nail avulsion with RV4104A ointment (class I medical device containing 40% urea) followed by ciclopirox olamine 1% cream for 8 weeks and ciclopirox 8% nail lacquer for 25 weeks (SEQ group) to amorolfine 5% nail lacquer for 36 weeks (AMO group).

Men and women aged 18–70 years with distal-lateral or lateral subungual onychomycosis caused by *T. rubrum* were included. Patients had to have onychomycosis affecting at least one big toenail without matrix involvement and showing between 25 and 60% of clinically infected nail area.

Patients were evaluated at week 3, week 11, week 36 and week 48. The primary efficacy criterion was complete cure, which comprised clinical cure (i.e. disappearance of all lesions on each nail or residual disease of no more than 10% of the original total diseased surface) and negative mycology at week 48.

A **cost-effectiveness analysis** was performed, using the primary endpoint as the efficacy measure. The pharmacoeconomic evaluation was conducted from the payer's perspective in each country (France and Tunisia). Since both groups followed the same evaluation process, there was no difference between groups either for compliance or for study discontinuation, and only few non-serious AEs occurred, only drug acquisition costs were included. Local public prices were computed in each country and converted into euros if needed using appropriate exchange rates.

b. Results

142 patients were randomized to the SEQ group (71) and AMO group (71). The baseline demographic characteristics (54.9% women, median age 46.5 years, 97.9% distal lateral subungual) and mycological results at inclusion (100% positive fungal culture and 96.5% filaments infection) were similar between groups.

SEQ treatment resulted in a significantly higher complete cure rate (36.6%) compared with amorolfine (12.7%, p = 0.001, OR = 3.98 [95% CI: 1.70; 9.30]) at week 48. **SEQ treatment was also associated with a significantly higher clinical cure** (53.5%) compared with amorolfine (16.9%, p = 0.001, OR = 5.66 [95% CI: 2.60; 12.31]). Patients in the SEQ group were significantly more likely to be clinically improved at week 36 than those treated in the AMO group (42.0 vs. 11.9%, respectively, p < 0.001, OR = 5.35 [95% CI: 2.22; 12.89]). Difference remained statistically significant after adjustment for centres and countries (p < 0.001). Similarly, mycological cure at week 48 was numerically higher in the SEQ group than in the AMO group at week 36, but with no statistically significant difference (57.8 vs. 46.5%, OR = 1.57 [95% CI: 0.81; 3.05]) (Supplementary Table 7).

Supplementary Table 7. Efficacy results

Efficacy variable	SEQ	AMO	P value

Complete cure rate at week 48	36.6%	12.7%	0.001
Clinical cure rate at week 48	53.5%	16.9%	0.001
Mycological cure rate*	57.8%	46.5%	NA
Clinical improve at week 36	42.0%	11.9%	<0.001

Notes: *Mycological cure values correspond to week 48 for SEQ and week 36 for AMO. | Acronyms: AMO: Amorolfine (5% nail lacquer for 36 weeks); NA: Not Applicable; SEQ: Sequential Treatment (RV4104A ointment followed by Ciclopirox olamine 1% cream for 8 weeks and Ciclopirox 8% nail lacquer for 25 weeks)

The local tolerability was good and very good for more than 90% of patients in each group at each visit. Discontinuation rates were higher in the AMO group (7.0%) than in the SEQ group (2.8%), mainly due to differences in the percentage of patients who discontinued due to lack of efficacy (4.2% in the AMO group vs. 0.0% in the SEQ group). Treatment compliance remained high during the entire treatment and was similar in both groups (94.6% in the AMO group vs. 95.2% in the SEQ group – PP population).

Cost-effectiveness analysis: Cost per completely cured patient of the SEQ treatment RV4104A ointment followed by ciclopirox olamine 1% cream and ciclopirox 8% film-forming solution versus amorolfine 5% nail lacquer alone was computed in each participating country. Quantities used were those defined according to the EPPM panel (permanent survey of the medical prescription). **Total cost per patient completely cured was shown to be about twice higher with amorolfine at € 76 than with SEQ treatment at € 33.**

c. Discussion

The sequential treatment involving urea-based ointment, nail debridement, ciclopirox olamine 1% cream, and ciclopirox 8% film-forming solution resulted in a higher complete cure rate and lower treatment cost per complete cured patient for toenail onychomycosis compared to amorolfine 5% nail lacquer alone. Thus, **the SEQ treatment involving ciclopirox 8% lacquer demonstrated greater efficacy and a better cost-effectiveness profile compared to amorolfine 5% lacquer.**

4. Pharmacoeconomic Assessment of Ciclopirox Topical Solution, 8%, Oral Terbinafine, and Oral Itraconazole for Onychomycosis (2006)

a. Objective and Methodology

The objective of the ***Gupta et al.*** "Pharmacoeconomic Assessment of Ciclopirox Topical Solution, 8%, Oral Terbinafine, and Oral Itraconazole for Onychomycosis" study (2006) was to evaluate the cost-effectiveness of the three onychomycosis treatment regimens approved

for use in dermatophyte toenail onychomycosis in Canada: continuous oral terbinafine, oral itraconazole pulse therapy, and ciclopirox nail lacquer 8%. *(138)*

This study adapted previously published economic models for onychomycosis, using costs in Canadian dollars and representative of the Canadian health care system. The model used 1-year cycles and a 3-year time horizon. After the first cycle, there were three possible outcomes: cure, relapse (where previously cured subjects show mycologic signs of infection), or treatment failure. It was presumed that subjects in the second cycle would continue to be treated with the same medication used during the first period. Similarly, subjects showing relapse or failure at the end of the second cycle were re-treated with the primary drug, providing a maximum of three treatments. A meta-analysis was used to determine mycologic cure rates for each regimen, and relapse rates were obtained from the medical literature for each treatment. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the expected cost per patient for each regimen by the expected cost per patient for the therapy with the lowest cost. Costs included drug acquisition and medical management. The main analysis assumed that two bottles of ciclopirox nail lacquer were required per treatment.

b. Results

Mean mycologic cure rates calculated in the meta-analyses were 75% for continuous terbinafine, 60% for itraconazole and 53% for ciclopirox lacquer.

The base case costs and mycologic cure rates from the meta-analysis were used as inputs for the cost-effectiveness analysis. Relapse rates after 3-4 years were 17% for continuous terbinafine, 21% for ciclopirox lacquer (assumed) and 36% for pulse itraconazole. The model, which included two potential retreatments, found that ciclopirox had the lowest expected cost per patient, followed by terbinafine. The ICER for terbinafine and itraconazole compared to ciclopirox were 1.24 and 1.63, respectively (Supplementary Table 8).

Supplementary Table 8. Resource use, costs ($CAN), and base case results

Parameter	Terbinafine*	Itraconazole (pulse)†	Ciclopirox‡
Dermatological consultation	1 ($ 37.50)	1 ($ 37.50)	1 ($ 37.50)
Return visits	2 ($ 46.00)	2 ($ 46.00)	2 ($ 46.00)
Mycology tests	1 ($ 18.30)	1 ($ 18.30)	1 (1$ 8.30)
Liver function tests	2 ($ 35.70)	2 ($ 35.70)	0 (0)
Blood count	2 ($ 10.40)	0 (0)	0 (0)
Medical management sum	$ 147.90	$ 137.50	$101.80
Drug acquisition	$311.39	$323.40	$197.89
Base case costs	$459.29	$460.90	$299.69
Mycological cure rate	0.75	0.60	0.53
Mycologic relapse	0.17	0.36	0.21
Cost/mycological cure	$612.38	$768.17	$565.45
Expected cost per patient	$746. 72	$983.42	$601.52
ICER	1.24	1.63	NA

Notes: *Terbinafine 250 mg/day for 12 weeks; †Itraconazole 400 mg/day, 1 week per month for 3 months (pulse); ‡Ciclopirox 8% nail lacquer daily for 48 weeks. | Acronyms: ICER: Incremental Cost-Effectiveness Ratio; NA: Not Applicable.

c. Discussion

The analysis demonstrated that ciclopirox nail lacquer is a cost-effective antifungal treatment within the Canadian healthcare system, owing to its lower drug acquisition costs compared to continuous terbinafine and pulse itraconazole.

5. Pharmacological analysis of nail lacquer to treat onychomycosis in Spain (2005)

a. Objective and Methodology

The objective of the ***Ribera Pibernat et al.*** "Pharmacological analysis of nail lacquer to treat onychomycosis in Spain" study (2005) was to determine the most cost-effective treatment for dermatophyte onychomycosis in Spain in 2004. *(139)*

A cost-effectiveness study was performed of the different topical treatments in nail lacquer formulation (ciclopirox water insoluble, amorolfine and tioconazole) for white superficial onychomycosis and/or mild distal onychomycosis using a Markov chain model. The therapeutic regimens consisted of recurrent cycles for a maximum of 30 months. Monotherapeutic alternatives and the option of non-treatment were also analysed. The treatment outcomes considered were cure, non-cure, and recurrence of onychomycosis. Mycologic cure was considered and defined as a negative result in a microscopic

examination and/or a negative culture. Treatment failure was defined as the persistence of at least one positive result in either of the two tests.

To the determine each treatment efficacy, a meta-analysis was performed on the treatment of superficial white onychomycosis and/or mild distal onychomycosis (involving 2-4 nails, affecting less than 80% of the nail plate, without onycholysis, and with preservation of the nail matrix).

The analysis was done from the perspective of the Spanish National Health System, meaning only direct medical costs were included. The costs included in each cycle for each therapeutic alternative were medical visit, treatment, and diagnostic testing costs.

b. Results

Results show that the most efficient strategy was to initiate treatment with 8% ciclopirox nail lacquer applied once daily (Supplementary Table 9). In this study, the ICER was defined as the additional cost required to increase the probability of success by 1 percentage point compared to the least expensive alternative, among the options that are not dominated by others.

The ciclopirox treatment option dominated the amorolfine and tioconazole alternatives, meaning it was associated with better health results and lower costs. In the threshold analysis of the probability of cure with ciclopirox, it was observed that when the probability of cure with ciclopirox is ≥ 34.16%, while keeping the other therapeutic alternatives unchanged, the ciclopirox nail lacquer strategy becomes the most efficient option.

Supplementary Table 9. Results of the Onychomycosis Treatment Strategy with Antifungal Nail Lacquers

Treatment	Placebo	Ciclopirox	Tioconazole	Amorolfine
Cost	€ 51.5	€ 103.0	€ 145.6	€ 272.6
Incremental cost	NA	€ 51.5	€ 42.6	€ 169.6
Efficacy	0.095	0.484	0.469	0.387
Incremental efficacy	NA	0.389	-0.015	-0.097
CE	541.58 €/EU	212.64 €/EU	310.27 €/EU	704.58 €/EU
ICER	NA	132.37 €/EU	Dominated	Dominated

Notes: ICER was defined as the additional cost required to increase the probability of success by 1 percentage point compared to the least expensive alternative, among the options that are not dominated by others. | Acronyms: CE: Cost-Effectiveness; EU: Efficacy Unit; ICER: Incremental Cost-Dffectiveness Ratio; NA: Not Applicable.

c. Discussion

The results of this study show that the most efficient therapeutic alternative for treating patients with superficial white onychomycosis and/or mild distal onychomycosis is topical treatment with ciclopirox 8% nail lacquer.

6. Treatment of Dermatophyte Toenail Onychomycosis in the United States: A Pharmacoeconomic Analysis (2002)

a. Objective and Methodology

The objective of the ***Gupta et al***. "Treatment of Dermatophyte Toenail Onychomycosis in the United States: A Pharmacoeconomic Analysis" study (2002) was to evaluate the cost-effectiveness of the most commonly used therapies for the management of dermatophyte toenail onychomycosis, *(136)* and update previously presented data from the ***Gupta et al.*** "Pharmacoeconomic analysis of Ciclopirox nail lacquer solution 8% and the new oral antifungal agents used to treat dermatophyte toe onychomycosis in the United States" (2000) study. *(137)*

The economic model was based on previously published models. The agents most frequently used to treat dermatophyte toenail onychomycosis in the United States in 2001 were oral terbinafine (continuous regimen), itraconazole (pulse and continuous regimens), and ciclopirox 8% nail lacquer and were used as comparators. Fluconazole and griseofulvin were also included in the analysis. A meta-analysis of studies published from 1966 to 2000 was performed to determine the efficacy of the 5 drugs included in the model. Efficacy was evaluated 1 year from the start of therapy for all treatments, with a 3-year time horizon. Possible outcomes at the end of 1 year from the start of therapy were mycologic cure (negative light microscopic examination and culture), relapse, or failure (positive mycology with either positive light microscopic examination, positive culture, or both). Patients who had a relapse or who failed the initial course of therapy had an equal chance of receiving treatment with terbinafine, itraconazole (pulse), or ciclopirox 8% nail lacquer. The analysis was conducted from a third-party payer perspective.

For each of the analysed drugs, the regimen cost analysis included the sum of drug acquisition costs, medical management expenses, and the costs associated with managing AEs. All costs were reported in US dollars.

b. Results

The mean time to mycologic cure was 11 months for griseofulvin (panel consensus); 10 months for itraconazole (continuous), 10 months for itraconazole pulse (panel consensus), 10 months for terbinafine, 10 months for fluconazole, and 8.5 months for ciclopirox 8% nail lacquer. The meta-analysis results used in the model are presented in Supplementary Table 10.

Supplementary Table 10. Average Mycological Cure, Clinical Response, and Relapse rates

	Mycological Cure Rate		Clinical Response Rate		Relapse Rate
Drug	Average	95% CI	Average	95% CI	
Griseofulvin	41.1 ± 20.4	1.2–81.0	33.7 ± 14.1	6.1–61.4	40 %

	Mycological Cure Rate		Clinical Response Rate		Relapse Rate
Drug	Average	95% CI	Average	95% CI	
Itraconazole (continuous)	66.3 ± 4.2	58.1–74.6	70.3 ± 4.2	62.1–78.5	21 %
Itraconazole (pulse)	70.8 ± 5.7	59.6–82.1	73.6 ± 4.6	64.6–82.7	10.4 %
Terbinafine	76.9 ± 4.0	69.2–84.7	73.6 ± 3.6	66.6–80.6	15 %
Fluconazole	65.6 ± 7.1	51.7–79.5	66.5 ± 11.7	43.6–89.5	4.4 %
Ciclopirox 8% lacquer	52.6 ± 4.2	44.4–60.7	52.4 ± 9.0	34.8–70.0	20.7 %

Notes: data based on the meta-analysis. | Acronyms: CI: Confidence Interval.

Ciclopirox 8% nail lacquer demonstrated the lowest regimen costs, lowest cost per mycologic cure, and the lowest cost per expected disease-free day (DFD) (Supplementary Table 11).

Supplementary Table 11. Pharmacoeconomic analysis

Parameter	Griseofulvin	Itraconazole (continuous)	Itraconazole (pulse)	Terbinafine	Fluconazole	Ciclopirox*
Total cost regimen	$ 1,470.70	$ 1,468.9	$ 841.08	$ 948.90	$ 1,005.24	$ 361.12
Mycological cure rate	0.411	0.663	0.708	0.772	0.656	0.526
Cost/mycological cure	$ 3,578.4	$ 2,215.60	$ 1,188.0	$ 1,233.90	$ 1,532.40	$ 686.50
Expected cost per patient	$ 2,305.30	$ 2,043.10	$ 1,286.00	$ 1,397.10	$ 1,365.30	$1,028.00
Expected nº DFDs	414	554	612	611	620	563
Cost per expected DFD	$ 5.56	$ 3.69	$ 2.10	$ 2.2	$ 2.20	$1.81
Relative CE	3.04	2.02	1.15	1.23	1.21	1.00
Incremental (marginal) CE ratio	Dominated by Ciclopirox	Dominated by Ciclopirox	5.3	7.7	5.9	NA

Notes: *Ciclopirox 8% nail lacquer. | Acronyms: CE: Cost-Effectiveness; DFD: Disease-Free Day.

c. Discussion

The pharmacoeconomic analysis suggests that ciclopirox 8% nail lacquer is a cost-effective option for the management of dermatophyte toenail onychomycosis.

An important limitation is that the mycologic cure and clinical response rates for the oral antifungal agents were obtained from trials in which the onychomycosis was generally

moderate to severe; on the other hand, the efficacy data for the ciclopirox 8% nail lacquer were derived from studies in which the onychomycosis may have been mild to moderate.

Ciclopirox nail lacquer is considered safe, with AEs limited to the application site and no known drug interactions. In contrast, oral antifungal agents also offer a favourable benefit-to-risk ratio for treating onychomycosis, but they can be associated with drug interactions and may cause systemic AEs.

7. Pharmacoeconomic analysis of Ciclopirox nail lacquer solution 8% and the new oral antifungal agents used to treat dermatophyte toe onychomycosis in the United States (2000)

a. Objective and Methodology

The objective of the ***Gupta et al.*** "Pharmacoeconomic analysis of Ciclopirox nail lacquer solution 8% and the new oral antifungal agents used to treat dermatophyte toe onychomycosis in the United States" study (2000) was to evaluate the relative cost-effectiveness of ciclopirox nail lacquer against the oral antifungal agents used in the United States for the treatment of dermatophyte toe onychomycosis. *(137)*

The study employed a 5-step economic model, considering the most commonly used agents for treating dermatophyte toenail onychomycosis in the United States. These included griseofulvin, itraconazole (both pulse and continuous regimens), terbinafine (continuous regimen), and fluconazole (weekly dosing), which were used as comparators. Ciclopirox nail lacquer topical solution 8% (continuous therapy) was the treatment under evaluation. A meta-analysis of studies published from 1966 to 1999 was performed to determine the efficacy of the 5 drugs included in the model.

Efficacy was evaluated 1 year from the start of therapy for all treatments, with a 3-year time horizon and under the third-party payer perspective. Patients who experienced treatment failure or relapse at the end of the first year were retreated (with equal probability of receiving any of the included drugs), while those who achieved a cure were monitored. The primary measure of efficacy was taken to be the mycologic cure rate.

For each of the five analysed drugs, the regimen cost analysis included the sum of drug acquisition costs, medical management expenses, and the costs associated with managing AEs. All costs were reported in US dollars. The relative cost-effectiveness ratios for the comparator drugs were determined with the drug comparator having the lowest expected cost per expected disease-free day being assigned a value of 1.

b. Results

Ciclopirox nail lacquer had the lowest drug acquisition cost of all comparators, lowest cost per mycologic cure, lowest cost of medical management and lowest cost of

regimen. No costs were associated with managing AEs because, in the studies conducted in the United States, no patients discontinued therapy temporarily or permanently.

The resulting ICER for ciclopirox were **5.68 $/ symptom-free day (SFD) vs itraconazole (pulse); 5.68 $/SFD vs terbinafine; and 6.14 $/SFD vs fluconazole**. When **compared to griseofulvin and itraconazole** (continuous treatment), **ciclopirox was the dominating treatment**, meaning it was associated with lower costs and better health results (Supplementary Table 12).

Supplementary Table 12. Pharmacoeconomic analysis results

Parameter	Griseofulvin	Itraconazole (continuous)	Itraconazole (pulse)	Terbinafine	Fluconazole	Ciclopirox*
Total cost of regimen	$ 1413.1	$ 1410.2	$ 811.7	$ 890.1	$ 966.8	$ 325.2
Mycological cure rate	0.411	0.663	0.708	0.772	0.656	0.526
Cost/mycological cure	$ 3438.2	$ 2126.9	$ 1146.4	$ 1153.0	$ 1473.7	$ 618.2
Expected cost per patient	$ 2198.5	$ 1951.3	$ 1232.1	$ 1311.	$ 1303.4	$ 953.6
Expected nº SFDs	415	554	612	612	620	620
Cost per expected SFD	$ 5.30	$ 3.52	$ 2.01	$ 2.14	$ 2.10	$1.69
Relative CE	3.13	2.08	1.19	1.27	1.24	1.00
Incremental (marginal) CE ratio	Dominated by Ciclopirox	Dominated by Ciclopirox	5.68	7.30	6.14	NA

Notes: *Ciclopirox 8% nail lacquer. | Acronyms: CE: Cost-Effectiveness; SFD: Symptom-Free Day.

c. Discussion

This analysis indicates that ciclopirox 8% nail lacquer can be considered a cost-effective treatment option for dermatophyte toe onychomycosis in comparison to the oral antifungal agents used for this indication, itraconazole (pulse), terbinafine, and fluconazole; and a dominating treatment option compared to griseofulvin and itraconazole (continuous).

A key limitation of this analysis is that the efficacy data for ciclopirox 8% nail lacquer solution from US trials are based on patients with mild to moderate dermatophyte toenail onychomycosis. In contrast, many trials conducted outside the United States using ciclopirox nail lacquer may have involved patients with a greater extent of nail plate involvement.