SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ONYTEC 80 mg/g medicated nail lacquer

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of medicated nail lacquer contains 80 mg of ciclopirox. Excipient with known effect:

One gram of solution of medicated nail lacquer contains 10 mg cetostearyl alcohol and 730 mg ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicated nail lacquer. Clear, colourless to slightly yellowish solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate fungal infections of the nails caused by dermatophytes, yeasts and moulds, without nail matrix/lunula involvement.

Onytec 80 mg/g medicated nail lacquer is indicated in adults.

4.2 Posology and method of administration

The medicated nail lacquer is intended for topical use on fingernails, toenails and immediately adjacent skin (perionychium, hyponychium).

Unless otherwise directed, Onytec nail lacquer is applied once a day in a thin layer to the affected nail/s after careful washing and drying. The medicated nail lacquer should be applied over the entire nail plate, 5 mm of surrounding skin and, if possible under the free edge of the nail. Onytec nail lacquer needs about 30 seconds for drying. 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 could be followed.

Onytec nail lacquer does not need to be removed by any solvent or abrasives (i.e. nail filing), it is sufficient to wash the nails. In case of unintentional removal by washing, Onytec nail lacquer can be applied again.

Regular removal of the nail free edge and any onycholitic material by nail clipping, is recommended. Treatment should be continued until complete mycological and clinical cure is achieved and healthy nail

has grown again. Normally, treatment duration of fingernails is for about 6 months while for toenails it is

about 9 to 12 months.

Being a topical treatment, no different posology is necessary for special population groups.

If the condition is refractory to therapy with Onytec nail lacquer and/or there is extensive involvement of one or several finger- and toenails, additional oral therapy should be considered.

Paediatric population

The safety and efficacy of Onytec in children and adolescents below 18 years of age have not yet been established. No data are available.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Mild to moderate onychomycosis is defined as fungal infection affecting up to 75 % of the nail surface, involvement of up to 5 nails, without involvement of nail matrix/lunula.

In case of severe onychomycosis and of predisposing factors, such as diabetes and immune disorders, alternative systemic therapy should be considered.

Duration of disease, extent of infection (involvement of the nail plate) and nail thickness (>2mm may indicate matrix involvement, and keratinaceous debris) may influence results of therapy.

Sampling of nails for fungal culture should be done 4 weeks after stopping the treatment to avoid interference with culture results by possible residues of active substance.

In case of sensitisation, treatment should be discontinued and appropriate therapy instituted.

Consideration of alternative treatment may be needed in patients with a history of diabetes, immune disorders, peripheral vascular disease, injury, painful or seriously damaged nails, skin conditions such as psoriasis or any other chronic skin condition, oedema, breathing disorders (Yellow nail syndrome).

The risk of removal of the unattached, infected nail, by the health care professional or during cleaning by the patient should be carefully considered for patients with a history of insulin dependent diabetes mellitus or diabetic neuropathy.

Contact with the eyes and mucous membranes should be avoided. Avoid biting or sucking nails during the treatment period with Onytec. The medicated nail lacquer is for external use only.

Nail polish or other nail cosmetic products should be removed before application of Onytec and should not be used on the treated nails.

Onytec contains cetostearyl alcohol which may cause local skin reactions (e.g.contact dermatitis).

This medicine contains 730 mg alcohol (ethanol) in each g of solution. It may cause a burning sensation on damaged skin.

The bottle should be capped when not in use. This product is flammable. Keep away from heat and open flame.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed. However, after application as recommended, the systemic bioavailability of ciclopirox is below 2%. No interactions are foreseen at the systemic level.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no clinical data on exposed pregnant women for ciclopirox. Animal studies have shown no direct or indirect harmful effect on pregnancy, embryonic development, development of the foetus and/or the birth. However, there are no adequate data on possible long-term effects on postnatal development (see section 5.3). As the systemic exposure to ciclopirox is negligible, the use of Onytec nail lacquer may be considered during pregnancy, if necessary.

Breast feeding:

It is unknown whether ciclopirox or its metabolites are excreted in human milk but at therapeutic doses of

Onytec nail lacquer no effects to the newborn/infants are anticipated. Fertility

No fertility studies have been performed in humans. A reduced fertility index in the rat was observed following oral administration (see section 5.3). These animal data are of negligible clinical relevance due to the low systemic exposure to ciclopirox following therapeutic treatment.

4.7 Effects on ability to drive and use machines

Onytec has no influence on the ability to drive and use machines.

4.8 Undesirable effects

According to clinical and post-marketing data, the most commonly reported adverse reactions during treatment are application site reactions, most of them mild and transient. Given the low amount of ciclopirox absorbed, no systemic adverse reactions are expected.

Tabulated list of adverse drug reactions

The adverse reactions reported are listed below using the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class (SOC)	Frequency	Adverse reaction (PT)
Skin and subcutaneous tissue disorders	Very rare	Erythema, skin exfoliation, skin burning sensation, pruritus
	Not known	Nail discolouration*, nail disorder, dermatitis contact**, rash, eczema
General disorders and administration site conditions	Not known	Application site pain, application site paraesthesia

** This reaction can also be attributed to the onychomycosis itself. ** Also beyond the application site.*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Onytec is for topical use. No overdose has been reported with the use of this product. In the event of accidental oral ingestion, an appropriate method of gastric emptying may be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals for dermatological use; Other antifungals for topical use; ATC code: D01AE14

The use of ciclopirox as an 8% concentration lacquer for the treatment of onychomycosis is well established. Onytec nail lacquer is an original, patented formulation of ciclopirox based on hydroxypropyl chitosan for delivery of the active ingredient to nails.

Onytec nail lacquer has a topical antimycotic action. The active ingredient is ciclopirox (pyridone derivative). In vitro, ciclopirox has been shown to be both fungicidal and fungistatic as well as having sporicidal activity. Ciclopirox has activity against a broad spectrum of dermatophytes, yeasts, moulds and other fungi. For most dermatophytes (Trichophyton species, Microsporum species, Epidermophyton species) and yeasts (Candida albicans, other Candida species) the MIC falls within the range of 0.9 to 3.9 µg/ml.

Table of susceptibility (strains relevant to illness)

Dermatophytes	*Trichophyton rubrum* *Trichophyton mentagrophytes* *Trichophyton spp* *Microsporum canis* *Epidermophyton floccosum*
Yeasts	*Candida albicans* *Candida parapsilosis*
Moulds	*Scopulariopsis brevicaulis* *Aspergillus spp* *Fusarium solani*

Clinical efficacy and safety

A systematic review and meta-analysis of all clinical data on both globally marketed ciclopirox 8% formulations (lacquer and hydrolacquer) confirms clinical efficacy and tolerability of this concentration as a treatment for onychomycosis.

Based on two studies (460 participants), compared with vehicle, ciclopirox 8% lacquer was more effective in achieving complete cure (risk ratio (RR) 9.29, 95% confidence interval (CI) 1.72 to 50.14) and mycological cure (RR 3.15, 95% CI 1.93 to 5.12). On their side, and based on two studies (490 participants), ciclopirox 8% hydrolacquer (Onytec) was more effective than the comparators ciclopirox 8% lacquer or amorolfine 5% in achieving complete cure (RR 2.43, 95% CI 1.32 to 4.48), but there is probably little or no difference between the treatments in achieving mycological cure (RR 1.08, 95% CI 0.85 to 1.37).

In comparison to vehicle alone ciclopirox lacquer was associated with an apparent increase in adverse events: those commonly reported were application reactions, rash, and nail alteration (e.g. colour, shape). However, the 95% CI suggested that the addition of ciclopirox to the vehicle lacquer produced no appreciable difference in the risk of events (RR 1.61, 95% CI 0.89 to 2.92;). With respect to ciclopirox 8% hydrolacquer (Onytec) no difference in the risk of adverse events was found in the comparisons carried out with ciclopirox 8% lacquer or amorolfine 5% (RR 0.60, 95% CI 0.19 to 1.92). The most common events were erythema, rash, and burning.

Ciclopirox 8% hydrolacquer (Onytec) has been investigated in a long-term clinical study in 467 patients with onychomycosis, compared to placebo and a commercially available formulation of ciclopirox 8% nail lacquer. All treatments were applied every day for 48 weeks to the infected nails. The patients were followed up for a further period of 12 weeks. All the efficacy assessments were done on a target great toenail.

Table of results at the end of follow-up (week 60)

End-point	Onytec nail lacquer	Placebo	Reference ciclopirox
Complete "cure"*	12.7%	1.3%	5.8%
"Responders"[#]	28.7%	14.7%	17.3%
"Improvement"[§]	46.5%	34.7%	39.7%
Decrease of diseased nail[¥]	36.3%	16.2%	21.8%

*conversion to negative of botth KOH microscopy and fungal culture, and 100% healthy appearing target great toenail

[#]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

[§] patients with at least 20% decrease of diseased nail area, as assessed by the blinded Evaluator, at the end of treatment versus baseline and conversion to negative KOH and culture

[¥] Decrease of diseased nail area to ≤ 10% of total as assessed by the blinded Evaluator

Onytec nail lacquer showed a better efficacy compared to placebo and to reference ciclopirox. A better effect was evidenced on the primary endpoint "cure" rate and on the key secondary endpoint "responder" rate, being 119% higher than the reference for cure rate (statistically significant, $p < 0.05$) and 66% higher for responder rate (statistically significant, $p < 0.05$).

In the clinical study no drug-related systemic adverse event was recorded.

Tolerability at the application site was continuously monitored throughout the treatment period. Signs and symptoms recorded were 2.8% and 7.8%, respectively, in the Onytec group; 8.6% signs and 16% symptoms were recorded in the reference group and 7.2% signs and 12.4% symptoms were recorded in placebo group. The most frequent sign recorded was erythema (2.8% in the Onytec group and 8.6% in the reference group). The most frequent symptom was burning (2.8% in the Onytec group and 10.7% in the reference group).

In a two arm, 48-week randomized, controlled, parallel-group clinical trial with a blinded evaluator, comparing ciclopirox 8% hydrolacquer (Onytec) applied once daily with amorolfine 5% nail lacquer given twice a week, 154 patients with onychomycosis were screened, with 120 randomised according to inclusion/exclusion criteria. The main efficacy variables were complete cure rate, treatment success and mycological cure, evaluated at 48 week time point in the intent-to-treat (ITT)

population. ‘Complete cure’ was defined as a composite of negative KOH microscopy and negative culture for fungal pathogens with no residual clinical involvement of the target toenail. ‘Treatment success’ was defined as negative KOH microscopy and negative culture for fungal pathogens as well as ≤ 10% residual involvement of the target toenail. ‘Mycological cure’ was defined as both negative direct microscopy and negative culture. All the efficacy variables (study endpoints) were evaluated on a target great toenail.

At week 48 the percentage of patients with complete cure, treatment success and mycological cure in the Onytec group, were consistently higher than in the amorolfine 5% group: Table: results at the end of treatment (week 48)

End-points	Onytec nail lacquer	Amorolfine 5% nail lacquer	Difference	95% confidence interval for the difference
Complete cure*	35.0%	11.7%	23.3%**	8.8 to 37.9
Treatment success#	58.3%	26.7%	31.7%**	14.9 to 48.4
Mycological cure$	100%	81.7%	18.3%**	8.5 to 28.1

* conversion to negative of both KOH microscopy and fungal culture, and 100% healthy target great toenail, as assessed by the blinded evaluator

conversion to negative of both KOH microscopy and fungal culture, and decrease of diseased nail area

to ≤ 10% of total as assessed by the blinded evaluator

$ conversion to negative of both KOH microscopy and fungal culture.

** $p<0.001$

In this clinical study no drug-related systemic adverse event was recorded.

5.2 Pharmacokinetic properties

Onytec nail lacquer has demonstrated good penetration properties through keratin. By achieving fungicidal concentrations at the site of infection, the active substance leads to irreversible binding to the fungal cell wall and this causes inhibition of the uptake of components needed for cellular synthesis and of the respiratory chain.

A very small amount of ciclopirox is absorbed systemically (<2% of the applied dose and the blood levels in a long-term study were 0.904 ng/ml (n=163) and 1.144 ng/ml (n=149) after 6 and 12 months of treatment, respectively. This shows that the drug exerts its activity particularly at the local level and the risk of possible interference with the normal body functions is negligible.

5.3 Preclinical safety data

Preclinical data up to a daily oral dose of 10 mg ciclopirox/kg revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. In reproduction studies in rats and rabbits no embryo-/fetotoxicity or teratogenicity was found. At the oral dose of 5 mg/kg, a reduced fertility index in the rat was observed. There was no evidence for peri- or postnatal toxicity, however possible long-term effects on progeny have not been investigated. Onytec nail lacquer exhibited no irritation in studies on local tolerance in rabbits and guinea pigs.

The chitosan derivative contained in the formulation is free of tropomiosine and did not exhibit allergenic potential in patients with shellfish allergy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethyl acetate

Ethanol (96%)

Cetostearyl alcohol

Hydroxypropyl-chitosan

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening the bottle: Keep the bottle tightly closed to avoid evaporation of the contents. After first opening use within 6 months.

6.4 Special precautions for storage

Keep the bottle in the outer carton, in order to protect from light. Do not refrigerate or freeze.

After first opening the container: Keep the bottle tightly closed to avoid evaporation of the contents.

For storage conditions after first opening of the medicinal product, see section 6.3

This product is flammable. Keep away from heat and open flame.

At temperature below 15°C the medicated nail lacquer may gel. Light flocculation or formation of a light sediment may also occur which can be reversed by warming up to room temperature (25°C) through rubbing the bottle between hands till the solution is clear again (about one minute). This has no impact on product quality or performance.

6.5 Nature and contents of container

Clear glass bottles with polypropylene screw caps which are fitted with a brush. Pack sizes: 3.3 ml, 6.6 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Almirall, S.A.

Ronda General Mitre, 151

08022 Barcelona

Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 16973/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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