New Zealand Data Sheet

1 PRODUCT NAME
Deolate 250 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Terbinafine 250 mg.

3 PHARMACEUTICAL FORM
Deolate 250 mg tablets are white, circular, biconvex tablets with “TF” on one side and a deep score on the other side. The tablet can be divided into equal doses.

Deolate tablets contain 250 mg terbinafine (as terbinafine hydrochloride 281.25 mg).

For a full list of excipients see Section 6.1.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Oral terbinafine is indicated in adults and children above 20 kg for the treatment of:

- Onychomycosis caused by dermatophyte fungi (fungal nail infection).
- Tinea capitis.
- Fungal infections of the skin including tinea corporis, tinea cruris, tinea pedis and
- Yeast infections of the skin caused by the genus Candida (for example Candida albicans)

Treatment of skin infections should only be considered if the site, severity or extent of the infection warrants oral treatment.

Unlike topical terbinafine, oral terbinafine is not effective in pityriasis versicolor.

4.2 Dose and method of administration
Deolate tablets are for oral administration only and should be taken at the same time each day with water, either on an empty stomach or after a meal.

The length of Deolate treatment differs according to the severity and indication of the infection.

Children

Weight of Child	Dosage
20 to 40 kg	125 mg once per day
More than 40 kg	250 mg once per day

Adults
250mg once per day.

Patients with renal impairment
Only use Deolate if there is no alternative treatment. Patients with creatinine clearance less than 50 mL per minute or serum creatinine of more than 300 micro mol per litre should take half the normal dose of Deolate (Please refer to Section 4.8 Undesirable Effects). Deolate is not suitable for patients with creatinine clearance values less than 20 mL per minute as there is no information on the use of oral terbinafine in this group.

Recommended treatment duration:

Skin infections
Cutaneous candidiasis: Two to four weeks.
Tinea corporis: Four weeks.
Tinea cruris: Two to four weeks.
Tinea pedis (interdigital, plantar/moccasin type): Two to six weeks.

Complete resolution of the infection symptoms and signs may not happen until several weeks following the mycological cure.

Hair and scalp infections
Tinea capitis: Four weeks.
Tinea capitis appears predominantly in children.

Onychomycosis
Six to twelve weeks.

Fingernail onychomycosis
Six weeks.

Toenail onychomycosis
Twelve weeks.

Longer treatment may be required in patients with poor nail outgrowth. The optimum clinical effect is observed a few months following mycological cure and the end of treatment. This is in relation to the time required for the outgrowth of a healthy nail.

Use of Terbinafine in the elderly
There is no evidence to indicate that elderly patients require different treatment doses. When tablets are prescribed for patients in this age group, the potential of pre-existing kidney or liver impairment should be considered (Please refer to Section 4.4 Special warnings and precautions for use).

4.3 Contraindications

- Identified hypersensitivity to terbinafine or to any of the excipients (Please refer to Section 6.1, List of Excipients).
- Patients with active or chronic liver disease.

4.4 Special warnings and precautions for use

Patients with impaired hepatic function:

Prior to prescribing Deolate tablets, an assessment of pre-existing liver disease should be completed (see Section 4.3). Hepatotoxicity may present in patients who have or do not have pre-existing liver disease therefore, monitoring of liver function after 4-6 weeks of treatment is recommended. Oral terbinafine should be immediately discontinued in the case of elevated liver function tests.

Rare occasions of liver failure with some leading to liver transplant or death, have been observed with the use of oral Terbinafine. In most of the liver failure reports, the patients had underlying systemic circumstances and an undecided causal connection with the administration of oral Terbinafine (Please refer to Section 4.8, Undesirable Effects).

Patients prescribed Deolate tablets should be cautioned to report any symptoms without delay of anorexia, dark urine or pale stools, fatigue, persistent nausea, right upper abdominal pain or jaundice or vomiting. Patients recognising with these symptoms must stop taking oral terbinafine and the patient's liver function should be evaluated immediately.

Patients with impaired renal function:

Only use Deolate if there is no alternative treatment.

Patients with creatinine clearance less than 50 mL per minute or serum creatinine of more than 300 micro mol per litre should take half the normal dose of Deolate (Please refer to Section 5.2 Pharmacokinetic Properties).

Deolate is not suitable for patients with creatinine clearance values less than 20 mL per minute, as there is no information on the use of oral terbinafine in this group.

Effect on blood:

Patients taking Deolate tablets are at risk of developing agranulocytosis, neutropenia and pancytopenia. Aetiology of any blood dyscrasias that appear in patients treated with Deolate tablets should be assessed and thought should be given for a potential change to the patient’s medication regimen, including the discontinuation of terbinafine tablet treatment. Patients prescribed Terbinafine tablets should be advised to report their infection symptoms.

Transient decreases in absolute lymphocyte counts (ALC):

Transient reductions in absolute lymphocyte counts (ALC) have been reported in controlled clinical trials. In placebo-controlled trials, eight terbinafine treated patients out of 465 patients (1.7%) and three placebo-treated patients out of 137 patients (2.2%) had reductions in ALC to below 1,000/mm^3 on more than two occasions. The clinical importance of this observation is unknown. Physicians should still contemplate monitoring complete blood counts in patients with known or suspected immunodeficiency for patients using Deolate tablet treatment for more than six weeks.

Effect on vision:

Changes in the ocular lens and retina have been reported following the use of terbinafine tablets in controlled trials in high dosage studies using monkeys. Refractile irregularities were observed in the retina at doses that were 30 to 60 times the human dose (non-toxic

effect level 50 mg/kg). The clinical significance of these changes is unknown. Further, the ocular effects in monkeys were not confirmed in humans in the placebo-controlled trials, where the incidence of ophthalmic abnormalities were lower in the terbinafine tablet-treated patients (1.1%) compared with those who received placebo (1.5%).

Dermatological effects:
There have been rare observations of serious skin reactions (for example, Stevens-Johnson Syndrome and toxic epidermal necrolysis). Treatment using Deolate tablets must be discontinued, if a skin rash develops.

Patients with pre-existing psoriasis may be at risk of an exacerbation.

Effect on lipids:
Increased levels of serum cholesterol were observed in chronic toxicity studies of oral terbinafine in rats, at a dosage of 309 mg/kg per day. This result was more evident in female rats in comparison to male rats. In the different studies, effects on triglycerides levels were inconsistent. In monkeys, a dose of 300 mg/kg per day amplified triglyceride levels and chylomicron concentrations. A dose of 250 mg per day in a small clinical study over eight weeks did not observe any measurable changes in the profile of the lipid plasma. In further clinical trials, there was no proof of any significant difference in the plasma lipid profile of patients.

CYP2D6 metabolism inhibition:
In vitro and *in vivo* studies have observed that CYP2D6-mediated metabolism is inhibited by terbinafine. Because of this, if patients are receiving concomitant treatment with medication primarily metabolized by this enzyme, they should be monitored if the medication co-administered has a reduced therapeutic window (for example, antiarrhythmics Class IC, beta-blockers, monoamine oxidase inhibitors (MAOIs) Type B, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs; for example, desipramine). Please refer to Section 4.5 Interaction with other medication and other forms of interaction.

4.5 Interaction with other medication and other forms of interaction

Effect of other medication on terbinafine:
The dosage of terbinafine tablets may need to be adjusted when co-administration is necessary as it is known that the plasma clearance of terbinafine may be accelerated by medications that induce metabolism and may be hindered by medications that inhibit cytochrome P450.

The following medications may increase the effect or terbinafine plasma concentration:

Medication	Effect on Terbinafine
Cimetidine	The clearance of terbinafine is decreased by 33%.
Fluconazole	The C_{max} of terbinafine is increased by 52% and the AUC is increased by 69% due to CYP2C9 and CYP3A4 enzyme inhibition.
Ketoconazole and Amiodarone	When concomitantly administered, an increase in exposure similar to Fluconazole may occur.

The following medications may reduce the effect or terbinafine plasma concentration:
The clearance of terbinafine is increased by 100% with rifampicin.

Effect of terbinafine on other medications:

Studies completed *in vitro* and in healthy volunteers, showed that terbinafine demonstrates insignificant potential for the inhibition or enhancement of the clearance of the majority of medications metabolized via the cytochrome P450 system (for example, oral contraceptives, terfenadine, tolbutamide or triazolam) with the exemption of those medications that are metabolized through CYP2D6 (refer to below).

The clearance of antipyrine or digoxin is not restricted by terbinafine.

There was no consequence of terbinafine on fluconazole pharmacokinetics. In addition, there was no interaction that was clinically relevant between terbinafine and the prospective co-medications cotrimoxazole (trimethoprim and sulfamethoxazole), theophylline or zidovudine.

There have been a few reports of menstrual irregularities in patients (for example, an irregular cycle or breakthrough bleeding) who have been administered terbinafine tablets alongside oral contraceptives, however, these irregularities remain within the related incidence of patients taking oral contraceptives only.

There have been spontaneous reports of increase or decrease in prothrombin times in patients concomitantly taking oral terbinafine and warfarin, however, a causal relationship between terbinafine tablets and these changes has not been established.

Terbinafine may amplify the effect or plasma concentration of the subsequent medications:

- ***Caffeine***

The removal of caffeine when administered intravenously was reduced by 19% when administered alongside terbinafine.

- ***Medications primarily metabolised by CYP2D6***

CYP2D6-mediated metabolism is inhibited by terbinafine which was shown in i*n vitro* and *in vivo* studies. This result may be of medical importance for compounds primarily metabolised by this enzyme, for example, particular members of the subsequent drug classes, antiarrhythmics class 1C, β-blockers, monoamine oxidase inhibitors (MAO-Is) Type B, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs), and if they also have a restricted therapeutic window (please refer to Section 4.4, Warnings and Precautions).

The removal of desipramine is decreased by 82% with terbinafine.

In studies with healthy individuals considered extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), the dextromethorphan/dextrorphan metabolic ratio was increased by terbinafine in urine by 16 times to 97 times on average. Therefore, terbinafine may induce extensive CYP2D6 metabolisers to inadequate metaboliser status.

Terbinafine may reduce the effect or plasma concentration of the following medications:
The clearance of cyclosporin is increased by terbinafine by 15%.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy
No adverse effects have been shown in foetal toxicity and fertility studies on terbinafine. Because clinical experience in pregnant women is especially limited, terbinafine should not be used during pregnancy unless the expected benefits outweigh any expected risks.

Use in Lactation
Oral treatment of Deolate tablets should not be administered to mothers who are breastfeeding as terbinafine is excreted into breast milk.

4.7 Effects on ability to drive and use machines
There is no information available on the effects of driving ability and using machinery when taking Terbinafine. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects
The subsequent undesirable effects have been noted throughout post marketing observation or clinical trials.

Adverse reactions are graded under title of frequency using the following principle: very common ≥ 10%; common ≥ 1% to < 10%; uncommon (≥ 0.1% to < 0.01%; rare ≥ 0.01% to < 0.1% and very rare < 0.01%, including isolated reports.

Frequency	**Description of Adverse Effect**
Blood and lymphatic system disorders	
Very rare:	Haematologic disorders (agranulocytosis, neutropenia, thrombocytopenia, transient decrease in haematocrit, haemoglobin or leukocytes) and allergic reactions (anaphylaxis).
Gastrointestinal disorders	
Very common:	Gastrointestinal symptoms (diarrhea, dyspepsia, feeling of fullness, loss of appetite, mild abdominal pain, nausea, vomiting, flatulence, anorexia, belching and abdominal distension).
General disorders	
Very rare:	Fatigue.
Hepatobiliary disorders	
Rare:	Transient increases in liver enzymes, hepatobiliary dysfunction (mostly cholestatic in nature), cholestatic jaundice, plus very rare instances of serious liver failure (including some with a fatal outcome, or requiring liver transplant).
Immune system disorders	

Very rare:	Anaphylactoid reactions (which includes angioedema), cutaneous and systemic lupus erythematosus.
Musculoskeletal and connective tissue disorders	
Very common:	Musculoskeletal reactions (arthralgia, myalgia).
Nervous system disorders	
Common:	Headache.
Uncommon:	Taste disturbances, taste loss (usually this may take several weeks to recover following discontinuation of terbinafine). Remote situations of extended taste disturbances have been observed. A reduction of food intake resulting in significant weight loss was observed in very few severe cases.
Very rare:	Dizziness, hypoaesthesia and paraesthesia.
Skin and subcutaneous tissue disorders	
Very common:	Rash, urticaria, pruritus, erythema (non-serious forms of skin reactions).
Very rare:	Hair loss (no causal relationship has been established), dermatitis exfoliative, dermatitis bullous, psoriasiform eruptions or exacerbation of psoriasis, serious skin reactions (for example, acute generalized exanthematous pustulosis, anaphylactoid reactions including angioedema, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). In the occasion of an allergic or severe skin reaction, oral terbinafine treatment should be discontinued.

Additional adverse effects from spontaneous post-marketing reports
The subsequent adverse effects have been observed in spontaneous post-marketing reports and are arranged by system organ classes. As these adverse effects are reported from a population of unknown size, it is not always possible to consistently estimate their occurrence.

Blood and lymphatic system disorders: anaemia.

Ear and labyrinth disorders: hypoacusis, impaired hearing, tinnitus, vertigo.

Eye disorders: visual impairment, vision blurred, visual acuity reduced.

Gastrointestinal disorders: pancreatitis.

General disorders and administration site conditions: influenza-like illness, pyrexia.

Immune system disorders: anaphylactic reaction, serum sickness-like reaction.

Investigations: blood creatine phosphokinase increased.

Musculoskeletal and connective tissue disorders: rhabdomyolysis.

Nervous system disorders: anosmia including permanent anosmia, hyposmia.

Psychiatric disorders: anxiety and depressive symptoms.

Skin and subcutaneous tissue disorders: photosensitivity reactions (for example, photodermatosis, photosensitivity allergic reaction and polymorphic light eruption) drug rash with eosinophilia and systemic symptoms (DRESS).

Vascular disorders: vasculitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There have been reports of several cases of overdose (of up to 5 g), which have resulted in the following side effects; dizziness, epigastric pain, headache and nausea.

The advised treatment of overdose involves the elimination of terbinafine, mainly by the administration of activated charcoal, and providing symptomatic supportive therapy, if required.

For the management of terbinafine overdose please contact the National Poisons Information Centre on 0800 POISON (0800 764 766) for advice.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral antifungal agent (ATC code D01B A02).

Terbinafine is an allylamine which has an extensive range of activity against fungal pathogens of the hair, nails and skin including dermatophytes such as Trichophyton (for example, T. mentagrophytes, T. rubrum, T. tonsurans, T. verrucosum and T. violaceum), Microsporum (for example, M. canis), Epidermophyton floccosum, and yeasts of the genera Candida (for example, C. albicans) and Pityrosporum. At reduced concentrations, terbinafine is fungicidal against dermatophytes, dimorphic fungi and moulds. Its activity against yeasts is either fungicidal or fungistatic, which is dependent on the species.

Terbinafine interferes exclusively with fungal sterol biosynthesis at an early stage. This results in a deficit of ergosterol and an intracellular increase of squalene, which results in fungal cell death. Terbinafine acts by inhibiting squalene epoxidase in the fungal cell membrane. The squalene epoxidase enzyme is not related to the cytochrome P450 system. When taken orally, terbinafine concentrates in the hair, nail and skin at quantities associated with fungicidal activity.

The metabolism of hormones and other medication is unaffected by terbinafine tablet treatment.

5.2 Pharmacokinetic properties

Terbinafine is absorbed well (more than 70 percent) following administration orally. The absolute bioavailability as an outcome of first-pass metabolism of terbinafine from terbinafine tablets is approximately 50 percent. An individual 250 mg oral dose of terbinafine concluded in a mean value of 1.3 microgram/mL peak plasma concentration within 1.5 hours of administration. At steady-state, in contrast to an individual dose, peak concentration of terbinafine was typically 25 percent higher and the plasma AUC had increased by a factor of 2.3. Due to the plasma AUC increase, an effective half-life of approximately thirty hours can be considered. Terbinafine bioavailability is affected by food on a moderate scale (i.e. AUC increase of less than 20 percent), but not enough to require adjustments to the dose.

Terbinafine binds effectively to plasma proteins at 99 percent. Terbinafine diffuses rapidly through the dermis and converges in the lipophilic stratum corneum. It is also sebum secreted, therefore reaching elevated concentrations in the hair, hair follicles, and sebum-rich skin. Furthermore, it is suggested that terbinafine is dispersed into the nail plate after commencing therapy within the first few weeks.

Terbinafine is extensively and rapidly metabolised by at least seven CYP isoenzymes with main contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation produces metabolites with nil antifungal activity, which are primarily excreted in the urine. No clinically significant age-dependent variations in steady-state plasma concentrations of terbinafine have been observed.

Pharmacokinetic studies of patients administered a single dose of terbinafine with renal impairment (creatinine clearance < 50 mL/min) or with liver disease that was pre-existing, have revealed that the terbinafine clearance may be decreased by about 50 percent.

5.3 Preclinical safety data

No noticeable toxic effects were seen in dogs and rats in longstanding studies of up to one year of oral dosages of up to about 100 mg per kg per day. At increased oral doses, the liver and possibly the kidneys were acknowledged as probably target organs.

In an oral carcinogenicity study that was completed over two years in mice, there was no neoplastic or additional abnormal conclusions attributable to treatment found that were made up to dosages of 130 mg/kg per day in males and 156 mg/kg per day in females. In an oral carcinogenicity study that was completed over two years in rats, there was an increase liver tumour incidence, which was observed in male rats at the maximum dosage level of 69 mg/kg per day. The differences, which may be related to peroxisome proliferation have been revealed to be species-specific, as they were not seen in the carcinogenicity study in mice or in additional studies completed in mice, monkeys or dogs.

In high dosage studies in monkeys, refractile irregularities were observed in the retina at the increased doses, with a non-toxic effect level of 50 mg/kg. These anomalies were connected with the presence of a terbinafine metabolite in the ocular tissue and withdrew once the drug was discontinued. These changes were not related with histological changes.

A typical battery of *in vitro* and *in vivo* genotoxicity examinations showed no evidence of mutagenic or clastogenic potential.

In studies completed in rabbits and/or rats, no adverse effects on fertility or other reproduction limitations were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, colloidal anhydrous silica, microcrystalline cellulose, sodium starch glycolate and hypromellose.

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage

Store at or below 25°C. Protect from light. Deolate tablets should be kept out of the reach and sight of children.

6.5 Nature and contents of container

Blister packs of 14, 56 or 84 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

REX Medical Limited
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9 DATE OF FIRST APPROVAL

18 October 2007

10 DATE OF REVISION OF THE TEXT

11 February 2020 V6

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.5	56 and 84 tablet pack sizes added.