

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Lamisil 250mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains terbinafine hydrochloride, equivalent to 250mg terbinafine.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

*Product imported from Spain:*

Circular, biconvex, bevelled-edge, white or off-white tablets about 11mm in diameter. One face is scored and the reverse is marked 'LAMISIL 250'.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Fungal infections of the skin caused by *Trichophyton* (eg. *T. rubrum*, *T. mentagrophytes*, *T. Verrucosum*, *T. Violaceum*). *Microsporum canis* and *Epidermophyton floccosum*.

Oral LAMISIL is indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection.

Onychomycosis (nail infections) caused by dermatophyte fungi.

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

### 4.2 Posology and method of administration

#### *Adults*

250mg once daily.

The bioavailability of terbinafine is not affected by food.

The duration of treatment varies according to the indication and the severity of the infection.

#### *Skin infections*

Likely durations of treatment are as follows:

Tinea pedis (interdigital, plantar/moccasin type):	2 to 6 weeks
Tinea corporis:	4 weeks
Tinea cruris:	2 to 4 weeks

### Onychomycosis

The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age.

In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.

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

### **Additional information on special population**

#### **Liver impairment**

Lamisil tablets are not recommended for patients with chronic or active liver disease (see section 4.4 Special warnings and precautions for use).

#### **Renal impairment**

The use of Lamisil tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

#### Children

There is no experience with oral Lamisil in children and its use cannot therefore be recommended.

#### Elderly

There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group.

#### Method of administration

The scored tablets are taken orally with water. They should preferably be taken at the same time each day and can be taken on an empty stomach or after a meal.

### **4.3 Contraindications**

Known hypersensitivity to terbinafine or to any of the excipients of Lamisil.

### **4.4 Special warnings and precautions for use**

#### **Liver Function**

Lamisil tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing Lamisil tablets, liver function test should be performed. Hepatotoxicity may occur in patients with and without pre-existing hepatic disease therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended. Lamisil should be immediately discontinued in case of elevation of liver function test. Very rare cases of serious hepatic failure (some with a fatal outcome, or requiring hepatic transplant) have been reported in patients treated with Lamisil tablets. In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Lamisil tablets was uncertain (see section 4.8 Undesirable effects).

Patients prescribed Lamisil tablets should be warned to report immediately any signs and symptoms of unexplained persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale stools. Patients with these symptoms should discontinue taking oral terbinafine and the patient's hepatic function should be immediately evaluated.

In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolised by this enzyme, e.g. certain members of the following drug classes, tricyclic antidepressants (TCA's),  $\beta$ -blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics class IC and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed, if the co-administered drug has a narrow therapeutic window (see 4.5 Interaction with Other Medicaments and Other Forms of Interaction).

Complete resolution of signs and symptoms of infection may not occur until several weeks after mycological cure.

Patients on terbinafine who develop a high fever or sore throat should be examined concerning possible haematological reaction.

### **Haematological effects**

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with Lamisil tablets. Aetiology of any blood dyscrasias that occur in patients treated with Lamisil should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Lamisil tablets.

### **Renal function**

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300  $\mu$ mol/L) the use of Lamisil tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).

### **Dermatological effects**

Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) drug rash with eosinophilia and systemic symptoms) have been very rarely reported in patients taking Lamisil tablets. If progressive skin rash occurs, treatment with Lamisil tablets should be discontinued. Lamisil should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as precipitation and exacerbation of psoriasis and cutaneous and systemic lupus erythematosus have been reported in a postmarketing setting.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### *Effect of other medicinal products on terbinafine*

The plasma clearance of terbinafine may be accelerated by drugs, which induce metabolism and may be inhibited by drugs, which inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of Lamisil tablets may need to be adjusted accordingly.

*The following medicinal products may increase the effect or plasma concentration of terbinafine:*

Cimetidine decreased the clearance of terbinafine by 33%.

Fluconazole increased the C<sub>max</sub> and AUC of terbinafine by 52% and 69% respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

*The following medicinal products may decrease the effect or plasma concentration of terbinafine:*

Rifampicin increased the clearance of terbinafine by 100%.

Information on other drugs concomitantly used with Lamisil resulting in no or negligible interactions

According to the results from studies undertaken *in-vitro* and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most drugs that are metabolised via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolised through CYP2D6 (see below).

Terbinafine does not interfere with the clearance of antipyrine or digoxin.

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further there was no clinically relevant interaction between terbinafine and the potential comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual irregularities have been reported in patients taking Lamisil tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

Terbinafine may increase the effect or plasma concentration of the following medicinal products:

Caffeine: Terbinafine decreased the clearance of caffeine administered intravenously by 19%.

Compounds predominantly metabolised by CYP2D6: *In vitro* and *in vivo* studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for compounds predominantly metabolised CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, especially if they also have a narrow therapeutic window (see 4.4 Special warnings and precautions for use).

Terbinafine decreased the clearance of desipramine by 82%.

In studies in healthy subjects characterized as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolisers to poor metaboliser status.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products: Terbinafine increased the clearance of ciclosporin by 15%.

## 4.6 Fertility, pregnancy and lactation

### Women of child-bearing potential

Some cases of menstrual irregularities have been reported in patients taking Lamisil tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

There are no data to support special recommendations for women of child-bearing potential.

### Pregnancy:

Foetal toxicity studies in animals suggest no adverse effects.

Since documented clinical experience in pregnant women is very limited, Lamisil tablets should not be used during pregnancy unless clinical condition of the woman requires treatment with oral terbinafine and the potential benefits for the mother outweigh any potential risks for the foetus.

**Breast-feeding:**

Terbinafine is excreted in breast milk and therefore mothers should not receive Lamisil treatment whilst breast-feeding.

**Fertility:**

There is no relevant information from human experience. Fertility studies in rats indicated no adverse findings in fertility or reproductive performance.

**4.7 Effects on ability to drive and use machines**

No studies on the effects of Lamisil tablets treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

**4.8 Undesirable effects**

In general Lamisil tablets are well tolerated. Side effects are usually mild to moderate and transient. The following adverse reactions have been observed in the clinical trials or during post marketing experience.

*Adverse drug reactions from clinical trials or post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ),.*

Table 1

<b>General disorders</b> Very rare	Fatigue
<b>Blood and the lymphatic system disorders</b> Very rare Not known	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia. Anaemia
<b>Immune system disorders</b> Very rare Not known	Anaphylactoid reactions (including angioedema, cutaneous and systemic lupus erythematosus). Anaphylactic reactions, serum sickness-like reaction
<b>Nervous system and psychiatric disorders</b> Common  Uncommon  Very rare Not known	Headache  Taste disturbances, including taste loss, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged taste disturbances have been reported. A decrease of food intake leading to significant weight loss was observed in very few severe cases.  Dizziness, paraesthesia and hypoaesthesia Anosmia

<b>Hepato-biliary disorders</b> Rare	Hepatobiliary dysfunction (primarily cholestatic in nature), including very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant). In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Lamisil tablets was uncertain.
<b>Gastrointestinal disorders</b> Very common	Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).
<b>Skin and subcutaneous tissue disorders</b> Very common Very rare	Non-serious forms of skin reactions (rash, urticaria). Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis)*. Psoriasiform eruptions or exacerbation of psoriasis. Hair loss, although a causal relationship has not been established.
<b>Musculoskeletal, connective tissue and bone disorders</b> Very common	Musculoskeletal reactions (arthralgia, myalgia).

**Other adverse drug reactions from post-marketing spontaneous reports:**

The following adverse drug reactions have been identified based on post-marketing spontaneous reports and are organized by system organ classes. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

**Table 2**

*Adverse drug reactions from spontaneous reports and literature (frequency not known)*

**Immune system disorders**

Anaphylactic reaction, serum sickness-like reaction.

**Nervous system disorders**

Anosmia including permanent anosmia, hyposmia.

**Eye disorders**

Vision blurred, visual acuity reduced. [46]

**Ear and labyrinth disorders**

Hypoacusis, impaired hearing [42]

**Vascular disorders**

Vasculitis.

**Gastrointestinal disorders**

Pancreatitis.

**Skin and subcutaneous tissue disorders**

Drug rash with eosinophilia and systemic symptoms. [46]

**Musculoskeletal and connective tissue disorders**

Rhabdomyolysis.

**General disorders and administration site conditions**

Influenza-like illness.

**Investigations**

Blood creatine phosphokinase increased.

## 4.9 Overdose

Based on the observed adverse effects in man, the main symptoms of an acute overdosage are likely to be gastrointestinal, e.g. nausea or vomiting. Gastric lavage and/or symptomatic supportive treatment may be required.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity versus yeasts is fungicidal or fungistatic depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane.

The enzyme squalene epoxidase is not linked to the cytochrome P-450 system.

Efficacy in tinea capitis has not yet been established.

Oral Lamisil is not effective in *Pityriasis versicolor*.

### Onychomycosis

The efficacy of Lamisil Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials (SFD301, SF5 and SF1508).

Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).

In a second toenail study of dermatophytic onychomycosis, in which non-dermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.

The mean time to treatment success for onychomycosis was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing Lamisil therapy, the clinical relapse rate was approximately 15%.

**Fungal infections of the skin (tinea corporis, tinea cruris, tinea pedis) and yeast infections of the skin caused by the genus *Candida* (e.g. *Candida albicans*) where oral therapy is generally considered appropriate owing to the site, severity or extent of the infection**

Three controlled, double blind, randomised, multicenter studies 5OR (4 week study), 6-7OR (4 week study) and 11-21OR (6 week study), evaluated efficacy and safety of Lamisil tablets in the treatment of Tinea corporis and cruris.

Two double blind, placebo controlled studies (85OR, 7OR) evaluated the efficacy of Lamisil 125mg b.i.d. in patients diagnosed with Tinea corporis/cruris. The studies included a total of 43 patients randomised to Lamisil and 45 on placebo. There was no significant difference in terms of demographic and anamnestic data within groups. Efficacy, demonstrated by negative mycology tests and a reduction in clinical symptomatology, was evaluated at 4 weeks and at the follow-up examination. In both studies, minimal efficacy was demonstrated in patients treated with placebo compared to the efficacy of orally administered Lamisil at the end of therapy and at follow up.

The third study (11-21OR), a 6 weeks, double blind, randomised, multicenter study compared efficacy and safety of Lamisil 125mg b.i.d. to griseofulvin 250mg b.i.d. One hundred twenty six (126) patients in each group were included in the efficacy analysis. This study showed high rate of mycological cure, reduction in signs and symptoms in the Lamisil treated study arm and significantly better (93-94%) overall efficacy at the end of therapy and at follow up of Lamisil 125mg b.i.d. compared to 86-87% overall efficacy of comparator.

In summary, Lamisil 125mg b.i.d. administered for the period of 4-6 weeks demonstrated statistically superior efficacy compared to placebo and marketed drug griseofulvin in the treatment of Tinea corporis/cruris in the above major efficacy studies.

In a double blind, placebo controlled 4 weeks study SF 00438, Lamisil 125 b.i.d was compared to placebo in patients with cutaneous candidiasis. Twenty one patients were randomised to each treatment arm, of which 19 were evaluated respectively. Of those, 29% of patients in the treatment arm and 17% of patients on placebo demonstrated mycological cure at the end of treatment and 67% of Lamisil treated patients had negative mycological results at the end of follow up. Given the above response rates, 2 weeks therapy of Lamisil should be the minimum duration of treatment period and approximately half of the patients would require 3-4 weeks of treatment to achieve cure.

Two double blind, controlled studies compared Lamisil 125mg b.i.d. to placebo (39-40OR) and to griseofulvin 250mg b.i.d. (20OR) in the treatment of Tinea pedis. Both studies recruited patients with chronic, recurrent disease. In the study 39-40OR, 65% of patients on Lamisil reported mycological cure at follow up whereas none of the placebo treated patients responded. In the study 20OR, Lamisil was shown to be highly effective with 88% of cure at follow up after 6 weeks therapy compared to 45% of patients on griseofulvin. These patients when observed after 10 months reported 94% cure rate, compared to 30% efficacy of griseofulvin in the same patient population.

**Table 12-1 Major efficacy studies – Tinea corporis/cruris, Tinea pedis, Candida infections**

Study	Type	Drug	No. of evaluable patients	Dropouts	Mycological results % negative		Clinical results	
					End Rx	F/up	End Rx	F/up
5OR	4wk DB-placebo	Lamisil 125	13	4	73	89	54	62
		b.i.d Placebo	15	2	0	0	0	0
6-7OR	4wk DB-placebo	Lamisil 125	33	7	97	97	89	91
		b.i.d Placebo	33	3	29	37	12	12
11-21OR	6wk 125 b.i.d. DB-	Lamisil 125	126	13	97	100	93	94
		b.i.d Griseofulvin	126	16	90	94	87	86
SF 00438	2wk DB-placebo	Lamisil 125	19	3	29	67	11	47
		b.i.d Placebo	19	3	17	47	11	11
39-40OR	6wk 125 b.i.d. DB-placebo	Lamisil 125	23	0	68	77	59	65
		b.i.d Placebo	19	0	14	0	0	0
20OR	6wk 125 b.i.d. DB-	Lamisil 125	16	2	94	100	75	88
		b.i.d Griseofulvin	22	6	27	55	27	45
		250 b.i.d						

## 5.2 Pharmacokinetic properties

Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from Lamisil tablets as a result of first-pass metabolism is approximately 50%. A single oral dose of 250 mg terbinafine resulted in a mean peak plasma concentration of 1.3 microgram/mL within 1.5 hours of administration. At steady-state (70% steady state is achieved in approximately 28 days), in comparison to a single dose, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3. From the increase in plasma AUC an effective half-life of ~30 hours can be calculated. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dose adjustments. When given orally, the drug accumulates in skin and nails at levels associated with fungicidal activity.

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum rich skins. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks of commencing therapy.

Terbinafine is metabolised rapidly and extensively by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. No clinically relevant age-dependant changes in pharmacokinetics have been observed. Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days.

Single dose pharmacokinetics studies in patients with renal impairment (creatinine clearance < 50 mL/min) or with pre-existing liver disease have shown that the clearance of Lamisil tablets may be reduced by about 50%.

## 5.3 Preclinical safety data

In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100mg/kg a day. At high oral doses, the liver and possibly also the kidney were identified as potential target organs.

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumours was observed in males at the highest dose level of 69mg/kg a day. The changes which may be associated with peroxisome proliferation have been shown to be species –specific since they were not seen in the carcinogenicity study in mice or other studies in mice, dogs or monkeys.

During high dose studies in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic levels 50mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in the ocular tissue and disappeared after drug discontinuation. They were not associated with histological changes.

An 8-week oral study in juvenile rats provided a no-toxic-effect level (NTEL) of close to 100 mg/kg/day, with the only finding being slightly increased liver weights, while in maturing dogs at  $\geq 100$  mg/kg/day (AUC values about 13 x (m) and 6x (f) those in children), signs of central nervous system (CNS) disturbance including single episodes of convulsions in individual animals were observed. Similar findings have been observed at high systemic exposure upon intravenous administration of terbinafine to adult rats or monkeys.

A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.

No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Magnesium stearate  
Colloidal silica anhydrous  
Hypromellose  
Microcrystalline cellulose  
Sodium carboxymethyl starch (potato without gluten)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

The shelf-life expiry date of this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

### **6.4 Special precautions for storage**

Store in the original package in order to protect from light.  
Do not store above 30°C.

### **6.5 Nature and contents of container**

PVC/ aluminium calendar blister packs containing 28 tablets

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 PARALLEL PRODUCT AUTHORISATION HOLDER**

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## **8 PARALLEL PRODUCT AUTHORISATION NUMBER**

PPA1328/120/002

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25<sup>th</sup> October 2013

## **10 DATE OF REVISION OF THE TEXT**