PHARMACEUTICAL COMPOSITIONS CONTAINING TERBINAFIN AND USE THEREOF

The invention relates to pharmaceutical compositions of terbinafine, in particular solid dosage forms for oral administration, and their use, in particular in the intermittent treatment of fungal infections, especially onychomycosis.

Terbinafine is known from e.g. EP-A-24587. It belongs to the class of allylamine anti-mycotics. It is commercially available under the trademark Lamisil^{R}. Terbinafine is effective upon both topical and oral administration, in a wide range of fungal infections. Terbinafine is particularly useful against dermatophytes, contagious fungi that invade dead tissues of the skin or its appendages such as stratum corneum, nail, and hair.

Terbinafine may be in free base form or in e.g. pharmaceutically acceptable salt form, e.g. the hydrochloride, lactate, ascorbate or malate, e.g. L.(+)-hydrogen malate form. It preferably is in the hydrochloride acid addition salt form. An acid addition salt form may be prepared from the free base form in conventional manner and vice-versa.

Nail fungi make their home in the nail bed, shielded by the hard outer nail. Thus once the infection is established under the nail, the nail itself provides the fungus with a protective environment that allows it to grow. The effects of these fungi on the nails may be unsightly, seriously complicate foot-care, have a deleterious impact on patients' overall quality of life and well-being and impair the patients' ability to work. If left untreated, the fungi can deform toenails permanently and lead to pain on walking. Additionally the fungi can lead to fissures in the skin, encouraging bacterial infection. Serious complications as a result of these infections may occur in people suffering from diabetes such as diabetic foot syndrome, including primary disease-related complications, e.g. gangrene that, ultimately, can be life-threatening or require amputations. Other high-risk patient sub-groups include patients infected with human immunodeficiency virus (HIV), patients with acquired immunodeficiency syndrome (AIDS), and patients with other types of immunosuppression, e.g. transplant recipients and patients on long-term corticosteroid therapy.

There is an increased prevalence of onychomycosis in the elderly (up to 30 % by age sixty). Microsporum, Trichophyton such as Trichophyton rubrum or Trichophyton mentagrophytes, and Epidermophyton such as Epidermophyton floccosum are those

microorganisms commonly involved. These infections are conveniently discussed according to the sites of the body involved. Diagnosis is confirmed by demonstrating the pathogenic fungus in scrapings of the lesions, either by microscopic examination or by culture. Across medical disciplines, onychomycosis is well recognized as being arduous both to diagnose and to manage, particularly in the aged.

Terbinafine is particularly useful to treat toenail and fingernail onychomycosis due to dermatophytes (e.g. tinea unguium). Indeed terbinafine has opened up treatment for tinea unguium caused by Trichophyton. For example The Merck Manual [1987] states that treatment of toe-nails should be discouraged with the previously used standard griseofulvin, because 1 to 2 years treatment is required, recurrence is usual and complete cure unlikely.

For the treatment of onychomycosis and other uses, terbinafine is normally administered as an immediate release tablet form containing 125 mg or 250 mg terbinafine (base equivalent) once daily. Such a tablet sold under the trademark Lamisil^R releases terbinafine to the extent of at least 80 % over a 30-minute period as measured by standard in vitro dissolution studies, e.g. at pH 3 using the paddle method. This is an example of an immediate release form. Terbinafine treatment over 12 weeks is required (hereinafter referred to as the "original treatment period"). The progress of its clinical effectiveness may be seen with growth of the healthy nail, pushing out and replacing the diseased unsightly nail-containing debris and dead fungus. About 10 months is needed for a totally new toe-nail to form.

Although terbinafine is generally regarded as safe like any prescription drug, adverse events associated with its use have been reported. As described in the Physicians' Desk Reference, there have been a number of adverse events recorded, e.g. headaches, gastrointestinal symptoms (including diarrhea, dyspepsia, abdominal pain, nausea and flatulence), liver test abnormalities, e.g. enzyme abnormalities, dermatological symptoms such as pruritis, urticaria and rashes, and taste disturbances, e.g. loss of taste. These adverse events are in general mild and transient. Further adverse events include symptomatic idiosyncratic hepatobiliary dysfunction (e.g. cholestatic hepatitis), severe skin reactions such as Stevens-Johnson syndrome, neutropenia and thrombocytopenia. Yet further adverse events may include visual disturbances such as changes in the ocular lens and retina, as well as allergic reactions including anaphylaxis, fatigue, vomiting, arthralgia, myalgia and hair loss.

Terbinafine is a potent inhibitor of CYP2D6 and may cause clinically significant interactions when co-administered with substrates of this isoform such as nortriptyline, desipramine, perphenazine, metoprolol, encainide and propafenone. Hereinafter any and all these events are referred to as "Adverse Events".

Various pharmacokinetic and biopharmaceutical properties of terbinafine are known. Thus terbinafine is well absorbed. Peak drug plasma concentrations (C_{max}) of about 1 μg/ml appear within 2 hours after administration of a single 250 mg terbinafine dose. The area under the curve over 24 hours (hereinafter AUC) is about 4.56 μg.hour/ml. A moderate increase in AUC is apparent when terbinafine is administered with a meal. In patients with renal impairment (e.g. creatinine clearance up to 50 ml /min) or hepatic cirrhosis the clearance of terbinafine is reduced by approximately 50 %. In the steady state, e.g. when the troughs and peaks are constant after dosing extending over several days, in comparison to the single dose, the peak terbinafine blood concentration (C_{max}) is 25 % higher and the AUC increases by a factor of 2.5. This is consistent with an effective half-life for terbinafine of about 36 hours.

Pharmacokinetic and absorption properties have been disclosed in e.g. J. Faergemann et al., Acta Derm. Venereol. (Stockh.) 77 [1997] 74-76 and earlier articles. Little has been disclosed on steady-state pharmacokinetics and pharmacokinetics on cessation of steady-state treatment. Although some low aborption was found to occur in the lower gastrointestinal tract, the main site of absorption of terbinafine is not precisely known and as indicated above there is no clinically proven correlation of effect with pharmacokinetic profile.

Further, despite the very major contribution to antimycotic therapy which terbinafine has brought, the reported occurrence of undesirable Adverse Events has been an impediment to its wider oral use or application. The particular difficulties encountered in relation to oral dosing with terbinafine have inevitably led to restrictions in the use of terbinafine therapy for the treatment of relatively less severe or endangering disease conditions, e.g. tinea pedis.

While numerous pharmaceutical compositions for topical and oral administration have been proposed, there still exists a need for commercially acceptable terbinafine formulations for oral administration with good patient convenience and acceptance, especially for children and the elderly. One particular difficulty in the formulation of terbinafine in oral pharmaceutical compositions is its unpleasant, e.g. bitter taste, and/or low physical integrity in free base form. Further, some patients may suffer from taste disturbance or taste loss.

It has now been found that, surprisingly, **terbinafine has a beneficial pharmacodynamic profile even in situations of high dosage load.** It may therefore be administered without untoward effect on e.g. the liver in higher daily dosage used intermittently and for a shorter duration of time than previously contemplated for the treatment of fungal infections such as onychomycosis or fungal sinusitis, yielding the unexpected result of equal or improved therapeutic outcomes from less total drug exposure, thus resulting in an overall dose of less drug than with previously known, e.g. continuous treatments, e.g. of about 30 % less. Thus the present invention enables reduction of terbinafine treatment times and overall dosing over the full treatment period required to achieve effective therapy, thereby reducing the exposure time to terbinafine and improving the global safety profile.

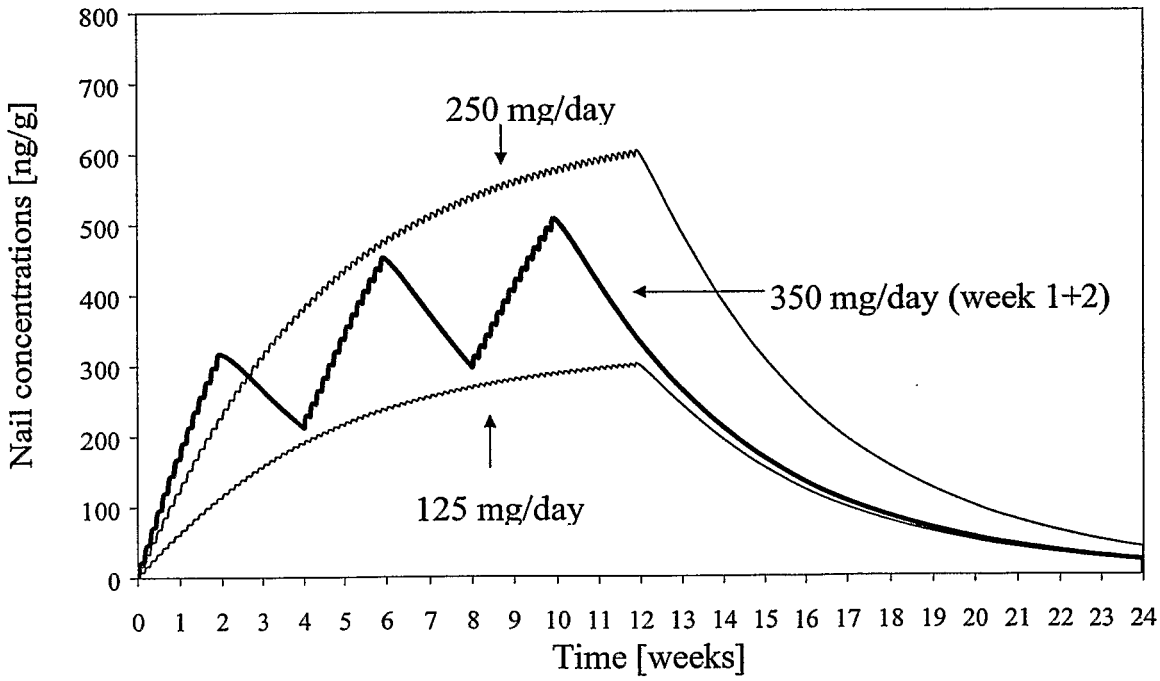
In addition it permits closer standardization as well as optimization of on-going daily dosage requirements for individual subjects receiving terbinafine therapy as well as for groups of patients undergoing equivalent therapy. By closer standardization of individual patient therapeutic regimens, dosaging parameters for particular patient groups, as well as monitoring requirements, may be reduced, thus substantially reducing the cost of therapy. Further, the antifungal activity of terbinafine being not just fungistatic but fungicidal, it may be used intermittently and administered for a short duration of time while nevertheless being curative, thus largely avoiding the need for prophylactic repeat treatment once mycological cure has been obtained and achieving increased efficacy without corresponding side effects.

The beneficial pharmacodynamic profile of terbinafine appears e.g. from tolerability studies upon high dosage over a short time duration. This is shown in e.g. standard tolerability or pharmacokinetic studies wherein terbinafine in immediate release form, such as a tablet, is administered at dosages higher than usual, namely tolerability studies in beagle dogs effected perorally (p.o.). Pharmacokinetic parameters (toxicokinetics), e.g. t_{max}, C_{max}, C_{max}/dose and AUC are measured. The following parameters are also monitored: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, calcium, chloride, total cholesterol, creatine kinase, creatinine, glucose, inorganic phosphorus, magnesium, potassium, sodium, total bilirubin, total protein, triglycerides and urea, as well as gamma glutamyltransferase (GGT). It was found that after a single peroral administration to male dogs of one standard tablet of terbinafine hydrochloride (125 mg base equivalent) at a

mean dose of 12.0 ± 0.3 mg/kg terbinafine (base equivalent), the values determined for t_{max}, C_{max} and C_{max}/dose were, respectively: 1 h; 199 ± 85 ng/ml; and 16.6 ± 7.2 (ng/ml)/(mg/kg).

Further, it could now be surprisingly determined in extensive computer modeling studies that e.g. in the treatment of onychomycosis, an intermittent dosing of e.g. 350 mg/day terbinafine (base equivalent) administered in 3 cycles, of 14 days on and 14 days off, would result in concentrations in the nail falling between the concentrations achieved with a continuous daily therapy over 12 weeks of, respectively, 125 mg/day, which is known to be less efficacious, and 250 mg/day, which is known to be highly efficacious, in onychomycosis treatment (see Figure). Therefore, it can be concluded that intermittent treatment in the above regimen, or variants thereof, would be expected to produce efficacy in patients.

Figure



The modeling is effected based on the following principles:

a) Terbinafine plasma concentrations following multiple oral administration is simulated on the basis of known population pharmacokinetic parameters upon continuous therapy [J. Nedelman et al., J.Clin.Pharmacol. 36 (1996) 452-456; J. Nedelman et al., Biopharm.Drug Dispos. 18 (1997) 127-138; and J. Nedelman et al., Eur.J.Drug Metab.Pharmacokinet. 22 (1997) 179-184]. The model incorporates a central, a rapidly equilibrating (shallow) and a slowly equilibrating (deep) peripheral compartment. Drug input into the central compartment is described as a zero order absorption process.

Elimination is, as is usual, assumed to occur from the central compartment; and
b) a linear relationship is then established between observed nail concentrations [J. Faergemann et al., Acta Derm.Venereol. 73 (1993) 305-309] and the model-predicted drug amount in the deep peripheral compartment. Hence the drug amount in the deep compartment is a suitable predictor for terbinafine nail concentrations.

Accordingly the invention provides a novel **method of treatment of fungal infection with terbinafine by administration of high doses over a short period of time,** preferably in a cyclical manner, thereby reducing total overall drug intake and further, it has now also become possible to devise corresponding **oral galenical formulations for delivering high drug loads in a short time span** which would not usually be readily contemplated, such as appropriate coated and/or multiparticulate formulation systems.

In **one embodiment,** the invention therefore provides a novel terbinafine dosing regimen method which meets or substantially reduces difficulties in terbinafine therapy hitherto encountered in the art. In particular it allows the use of pharmaceutical compositions which deliver terbinafine in sufficiently high concentrations to permit convenient oral once-a-day administration, while at the same time achieving improved safety and tolerability in terms of fewer Adverse Events. Specifically, in one aspect of this embodiment the present invention provides a **method of administering terbinafine to a subject in need of terbinafine treatment which comprises administering to the subject terbinafine in an intermittent cycle wherein the terbinafine is administered for more than one-third of the cycle,** hereinafter briefly named **"the method of the invention"**.

For example, the cyclically-administered terbinafine in a cycle may be administered daily or less frequently than daily, preferably daily, e.g. once a day. Preferably terbinafine is administered for a period of from more than one-third to two-thirds, preferably for about one-half of the cycle. A cycle may be e.g. from about 10 to about 50 days. Preferably a cycle is 28 days or a calendar month. Preferably terbinafine is administered daily for 14 consecutive days in a 28 days or monthly cycle, namely, for a 14-day period extending over roughly half a cycle. Preferably there are 3 or 4, especially 3 cycles. Oral administration is preferred.

It is to be appreciated that effective administration of terbinafine takes place during a time period extending over just a part, which is exceeding a third, of a cycle. The selection of the exact duration of a cycle, in particular, 28 days or a calendar month, is essentially based on considerations of convenience, taking into account, for example, the patient's gender.

If desired terbinafine may be administered every second or third day. Conveniently the total number of cycles is two or more, preferably 2 to 5, for example 4, especially 3. Preferably the intermittent dose of terbinafine is elevated as compared to daily dosages conventionally used, it is from about 300 mg to about 700 mg terbinafine (base equivalent), preferably from about 300 mg to about 450 mg, especially 350 mg per day. The safety of terbinafine at such a dose in the method of the invention is surprising. Especially preferred is a method of administering terbinafine to a subject in need of terbinafine treatment in three 28 days or monthly cycles of once daily oral administration of 350 mg/day of terbinafine (base equivalent) for 14 consecutive days of each cycle, thus resulting in about 30 % less total drug exposure (14.7 g) as compared with current dose/dose regimen (12 weeks, 250 mg/day; 21 g).

In a further aspect of this embodiment the invention provides for the **use of terbinafine as an active agent in the manufacture of a medicament** for use in the method of the invention.

For convenience such medicament, e.g. in the form of capsules, or stored in bottles, may be packaged into an appropriate box with instructions for use, e.g. for use in the above novel dosage regimen method. For example, the package may be a box containing three or four sets of 28 capsules containing 175 mg terbinafine (base equivalent), together with instructions for administration of 2 capsules per day for 14 consecutive days of the first 2 weeks of three or four successive 28-days periods or months.

In a further aspect of this embodiment the invention provides a **dosage pack containing a plurality of terbinafine compositions arranged to be dispensed** in the method or use of the invention, e.g. in non-continuous manner, e.g. where convenient together with instructions for use, preferably a **calendar pack**, optionally, for improved compliance, together with similarly-looking placebo compositions to be dispensed during the remaining part of each cycle when terbinafine is not administered.

Preferably the treatment period is for 3 or 4, especially 3 cycles in onychomycosis. This period represents the shortest treatment duration to date for treating this chronic infection. It is surprising that terbinafine in the method of the invention is at least as effective as with the original treatment but exhibits fewer Adverse Events than expected.

The above cyclical treatment may conveniently be used in combination with topical treatment with e.g. a cream containing terbinafine, e.g. 1 % by weight.

While pulse therapies with terbinafine have been envisaged in the past, they had either led to negative results (A. Tosti et al., J.Am.Acad.Dermat. 34 [1996] 595-600), and/or each proposed pulse was for a shorter duration with lower initial load and with more repeats (DE 100'17'996-A1) than with the present invention.

The above novel cyclical terbinafine dosing regimen method may be effected using conventional galenical forms, e.g. uncoated immediate release or sustained-release tablets (see e.g. Examples A and B hereafter).

However, in **another embodiment**, the invention further provides novel **galenical formulations of terbinafine** which may advantageously be administered in e.g. the method of the invention and allow particularly favourable systemic delivery of high once daily drug dosages in coated and/or multiparticulate form, resulting in low pharmakokinetic variability and few Adverse Events.

This follows from the further unexpected finding, in a study in dogs, of even lower pharmacokinetic variability when the standard 125 mg immediate release tablet is compared with an equivalent dose of terbinafine in a multiparticulate system (the coated minitablets of Example 4); it was found that the already low variability of the immediate release tablet is even further reduced in the multiparticulate system: while, as described above, at a mean dose of 12.0 ± 0.3 mg/kg terbinafine (base equivalent), after a single peroral administration of the standard tablet to male beagle dogs the values determined for mean t_{max}, C_{max}, C_{max}/dose and AUC were, respectively: 1 h; 199 ± 85 ng/ml; 16.6 ± 7.2 (ng/ml)/(mg/kg); and 526 ± 171 ng.hour/ml, with dogs receiving the coated minitablets at the same dosage of terbinafine, the values obtained were, respectively: 0.75 h; 246 ± 48 ng/ml; 20.5 ± 4.3 (ng/ml)/(mg/kg); and 644 ± 161 ng.hour/ml.

Thus a similar mean AUC [644 ± 161 v. 526 ± 171 ng.hour/ml] and a similar mean C_{max} [246 ± 48 v. 199 ± 85 ng/ml] were found for both galenical forms, but a much lower inter-subject variability of C_{max} [± 48 v. ± 85 ng/ml standard deviation in C_{max}] for the multiparticulate form v. the standard tablet. Furthermore, median t_{max} values were found to be 0.75 h and 1 h, respectively, for the multiparticulate and the standard form, with single values ranging from only 0.5 to 1 h for the multiparticulate form, but from 0.5 to 2 h for the standard form.

The pharmacokinetic parameters of both formulations were obtained using the same dog individuals and a crossover study design, hence possible period and inter-animal variability effects can be excluded. Plasma containing EDTA as anticoagulant was collected up to 48 hours post-dose, and bioanalysis was performed using HPLC with UV detection (measurement at 224 nm) after liquid-liquid extraction of the sample. The lower limit of quantification of the bioanalytical method was 1.00 ng/ml plasma. The dogs were fasted before administration. The washout period was one week between two administrations in the same dog. Feeding was performed 6 hours or more after dosing.

In one aspect of this other embodiment, the invention thus provides a novel **terbinafine solid dosage form for oral administration** which is suitable for minimizing effects associated with e.g. a high dosage load and **which is coated and/or multiparticulate,** e.g which comprises **coated tablets** providing less adverse events/side effects, **and/or multiple,** easily dispersed **particles** providing e.g. a reproducible and mainly food-independent transit through the gastrointestinal tract and a high surface area for reproducible dissolution of the drug substance, such as optionally coated minitablets or pellets in capsules, hereinafter briefly named **"the compositions of the invention"**.

Intermittent dosing allows administration of less total dose, but it involves administration of high daily doses: thus, the potential for transient adverse effects is enhanced, namely,

- at the systemic level, the higher plasma concentrations achieved (AUC, C_{max}) are leading to higher risk of adverse effects associated with pharmacokinetic variability or of e.g. centrally-induced taste disturbance; and
- at the local level, e.g. in increased risk of sensation of the bitter taste of terbinafine and/or of locally-induced taste disturbance.

The first concern above has now been found to be favourably addressed with multiparticulate systems, the second concern with appropriate coating, whereby these two aspects may advantageously be combined.

Taste disturbance or taste loss after terbinafine intake is a relatively rare and reversible Adverse Event that may, however, in single cases continue over an extended period, e.g. for longer than 12 weeks after cessation of treatment. Drug-induced taste disturbances can be divided into taste perversion (dysgeusia) and loss of acuity of taste (hypogeusia) or complete loss of taste (ageusia). In addition the sense of smell may be affected (hyposmia or anosmia). These changes, apart from their unpleasantness, can impair appetite, causing weight loss. Many drugs have been reported to cause taste disturbances or taste loss, including the antifungal agents griseofulvin and amphotericin B. AT_1 receptors may be involved in their pathogenesis. Terbinafine can also cause taste disturbances in a small number of patients: thus, in one large post-marketing surveillance study conducted in Austria, Germany, the Netherlands and United Kingdom in which patients were given 250 mg Lamisil^R (terbinafine) daily for a mean duration of 13.2 weeks, 186 instances of taste disturbances occurred altogether during the period of oral administration, representing a total incidence of 0.72 %, of which 0.37 % (97 patients) concerned primary dysgeusia (taste perversion) and 0.32 % (84 patients) ageusia (complete taste loss). All the patients recovered fully on discontinuing treatment.

In 7 further studies involving 959 Lamisil^R- and placebo-treated patients in 4 placebo-controlled and 3 dose-duration studies, the frequencies of reports of taste disturbance were 3.2 % in patients given Lamisil^R in the placebo-controlled studies, 1.2 % in those given Lamisil^R in dose-duration studies, and 0.6 % in placebo patients. Three of the patients had ageusia, the others had a variety of dysgeusia: salty, metallic, bland and bitter tastes. All patients made a complete recovery, with an average recovery time of 10.2 weeks. While annoying, none of the reported taste disturbances was considered to be harmful.

In rare instances the disturbances last longer than 12 weeks. The longest duration reported after discontinuation of drug was 2.5 years.

Therefore, while taste disturbances after terbinafine intake are rare and innocuous, they can be unpleasant and thus there is still a so far unmet need for novel means allowing treatment of fungal infection with terbinafine which eliminate or mitigate taste-related Adverse Events. The present invention also addresses this issue and provides a novel approach thereto.

The compositions of the invention are **adapted for release of the active substance terbinafine in the stomach**; for example, **in 0.04 M citrate buffer pH 3.0 at 37°C, terbinafine is released** from the composition **and dissolves within 30 minutes to the extent of at least 50 %**, e.g. at least 70 %, preferably at least 80 %.

The constituent particles of the multiparticulate system have a size ranging from about 0.5 mm to about 4 mm in diameter. They are not granules (typically of a particle size of up to about 0.5 mm) and include e.g. tablets, pellets or minitablets. Tablets, pellets or minitablets may be filled into capsules, e.g. hard gelatin capsules, or into sachets. Typically, one administration comprises a plurality of pellets or minitablets to achieve the desired overall dose of terbinafine per day.

The particles preferably are minitablets or pellets, i.e. they are presented formulated in a form that allows easy administration of a high load of active substance. The term "minitablets" denotes small tablets with an overall weight in their uncoated form of from about 3 to about 10 mg, e.g. from about 4 to about 7 mg, e.g. about 6 mg. The minitablets may have any shape convenient to the skilled person for tablets, e.g. spherical, e.g. with a diameter of from about 0.5 to about 4 mm, e.g. 1 to 4 mm or 2 to 4 mm; or cylindrical, e.g. having a convex upper face and convex lower face and e.g. with a cylindrical diameter and height which are, independently of each other, of from about 0.5 to about 4 mm, e.g. 1 to 3 mm; or they may be biconvex round minitablets, e.g. whose height and diameter are approximately equal and are from about 0.5 to about 4 mm, e.g. 1.5 to 4 mm, preferably 1.8 to 2.3 mm.

The minitablets may be uncoated, or coated with one or more layers of coating.

In one variant the minitablets are uncoated. In a further variant they are coated with only hydroxypropylmethyl cellulose (HPMC), e.g. HPMC 603 available as e.g. Pharmacoat^{R} 603 (see H.P. Fiedler, loc.cit. hereafter, p. 1172). In a further variant the coating(s) include(s) a taste-masking material, e.g. a polyacrylate, preferably an Eudragit^{R} such as Eudragit^{R}-E or Eudragit^{R}-RD100 or –RS/RL (see Handbook of Pharmaceutical Excipients, loc.cit. hereafter,

p. 362), especially Eudragit^{R}-E. In a further variant they are coated with a 3rd coating, e.g. with HPMC or polyethyleneglycols (PEG) to minimize further any interaction between minitablet and e.g. capsule. In a further variant the coating is devoid of plasticizer such as dibutyl sebacate, or the plasticizer is a fatty acid such as stearic acid, e.g. stearic acid NF (National Formulary, USP). In a further variant they are unencapsulated. In a further variant in the encapsulating material gelatin is replaced with alternative hard capsule materials, e.g. HPMC or starch.

Similar considerations apply mutatis mutandis for pellets as set out hereabove for minitablets; pellets preferably have a diameter of from about 0.5 to about 2 mm.

The compositions of the invention are formulated in a manner allowing optimal delivery, e.g. they are uncoated or, preferably, coated as appropriate. Accordingly, the invention also provides a **terbinafine solid dosage form for oral administration** which is **coated,** e.g. **dragées**, or **coated tablets, pellets or minitablets**. It further provides a **terbinafine solid dosage form for oral administration** which is **multiparticulate**, e.g. optionally coated **minitablets** or **pellets**, e.g. in capsules. It further provides a novel terbinafine solid coated and/or multiparticulate dosage form for oral administration **which has taste-masking properties and/or prevents taste disturbance or taste loss and associated adverse effects** such as **impaired appetite** and **weight loss**.

Suitable **coating materials** for the compositions of the invention include:

i) pharmaceutically acceptable cellulose derivatives such as ethyl cellulose (EC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellulose phthalate (HPMCP) or cellulose acetate phthalate (CAP);

ii) polyacrylates, especially polymethacrylates, preferably:

a) a copolymer formed from monomers selected from methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters;

b) a copolymer formed from monomers selected from butyl methacrylate, (2-dimethylaminoethyl)methacrylate and methyl methacrylate; or

c) a copolymer formed from monomers selected from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride;

e.g. those available from Röhm GmbH under the trademark Eudragit^{R};

iii) polyvinyl acetate phthalate (PVAP);

iv) polyvinyl alcohols;

v) polyvinylpyrrolidones (PVP);

vi) sugar such as saccharose or glucose, or sugar alcohols such as xylit or sorbit;

vii) shellac; and

viii) mixtures thereof.

Preferred cellulose derivatives i) are e.g. modified celluloses, e.g. hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropylmethyl cellulose, e.g. hydroxypropyl cellulose having a hydroxypropyl content of about 5 to 16 % by weight and of viscosity for 2 % w/w aqueous solutions of from about 2.0 to about 20 cps (= mPa.s), preferably from about 2.0 to about 6.0, e.g. 3.0 cps, e.g. hydroxypropyl methylcellulose (HPMC) (e.g. USP type 2910, 3 cps), available as e.g. Pharmacoat^R 603.

Especially preferred polyacrylic polymers ii) are:

1) the 1:1 copolymers formed from monomers selected from methacrylic acid and methacrylic acid lower alkyl esters, such as the 1:1 copolymers formed from methacrylic acid and methyl methacrylate available under the trademark Eudragit^R L, e.g. Eudragit^R L100, and the 1:1 copolymer of methacrylic acid and acrylic acid ethyl ester available under the trademark Eudragit^R L100-55;
2) the 1:2:1 copolymer formed from butyl methacrylate, (2-dimethylaminoethyl)-methacrylate and methyl methacrylate available under the trademark Eudragit^R E; and
3) the 1:2:0.2 copolymer formed from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride available under the trademark Eudragit^R RL; or the corresponding 1:2:0.1 copolymer available under the trademark Eudragit^R RS; or the 1:2:0.2 copolymer formed from ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride which is in combination with carboxymethyl cellulose and available under the trademark Eudragit^R RD.

The polyacrylates of group 3) above normally contain cationic ester groups. Examples of such cationic groups include dialkylaminoalkyl groups, e.g. dimethylaminoalkyl groups. Especially preferred cationic groups include quaternary ammonium groups, preferably a tri(alkyl)aminoalkyl group. Examples of such groups are trimethylaminoethyl ester groups. The polyacrylate may contain some carboxylic acid groups in free form or salt anions,

e.g. chloride anions in order to balance the cationic groups. The ratio of cationic groups to neutral groups is preferably from 1:10 to 1:50, e.g. from 1:10 to 1:30.

The polyacrylates of group ii) above have a mean molecular weight of about 50'000 to about 500'000, e.g. about 150'000.

Preferably, the coating materials comprise HPMC, Eudragits or sugar. It has been found that polyacrylates ii), especially Eudragit^R E, are particularly suitable for coating solid dosage forms comprising terbinafine in the form of the free base as well as in form of its salts, e.g. terbinafine hydrochloride, e.g. since a coating with Eudragit^R E does not easily dissolve at the neutral pH of the mouth, but only at pH values below 5, and thereby prevents the dissolution of the bitter tasting terbinafine until transfer to the stomach.

Coating materials as hereinabove defined may be used in admixture with further excipients conventional in coating formulations, for example talcum, magnesium stearate or silicon dioxide, for example synthetic amorphous silicic acid of the Syloid^R type (Grace), for example Syloid^R 244 FP, or colloidal silicon dioxide, e.g. Aerosil^R, e.g. Aerosil^R 200, or wetting agents, for example sodium dodecyl sulfate or the aforementioned polyethyleneglycols or polysorbates.

The coating materials may comprise additional excipients, for example **plasticisers** such as: triethyl citrate, e.g. Citroflex^R (e.g. from Morflex); triacetin; various phthalates, e.g. diethyl or dibutyl phthalate; diethyl or dibutyl sebacate; fatty acids or mixtures thereof, e.g. lauric, myristic, palmitic or stearic acid; alcohols, e.g. lauryl or stearyl alcohol; mixed mono- or diglycerides of the Myvacet^R type (Eastman), for example Myvacet^R 9-40; the polyethyleneglycols mentioned hereinbefore, for example having a molecular weight of approximately from 6000 to 8000; and also ethylene oxide/propylene oxide block copolymers of the poloxamer type, e.g. Pluronic^R (BASF) or Synperonic^R (ICI) type, such as Pluronic^R F68 (poloxamer 188) having a melting point of about 52°C and a molecular weight of about 6800 to 8975, or Synperonic^R PE L44 (poloxamer 124); pulverulent mould release agents, for example magnesium trisilicate; starch; or synthetic amorphous silicic acid of the Syloid^R type, for example Syloid^R 244 FP.

In one embodiment, the solid dosage forms may be coated by **one**, or preferably by **two or more coatings** which are applied one after the other. In one aspect, the solid dosage forms may be coated by a **first** (e.g. protective) **coating** applied directly upon the solid dosage form, e.g. comprising HPMC, and a **second** (e.g. taste-masking) **coating** applied upon the first coating, e.g. comprising Eudragit^R, preferably Eudragit^R E or Eudragit^R RD100, or ethyl cellulose.

In another aspect the solid dosage forms may comprise a **further coating**, e.g. a layer of **anti-sticking material** applied upon one of the above-mentioned coatings, e.g. comprising a colloidal silicon dioxide product, e.g. Aerosil^R, which may avoid adhesion of the solid dosage forms to each other or to the walls of the container material, e.g. a capsule.

Typically, overall coating weights for coating materials i) to v) range from about 0.5 to about 10 mg/cm^2 based on the surface area of the uncoated formulation, e.g. from about 1 to about 4 mg/cm^2, e.g. they are about 1.5 mg/cm^2. In particularly preferred embodiments, for a 350 mg terbinafine (base equivalent) coated tablet the coat weight is from about 3 to about 14 mg, and for a coated minitablet of about 6.5 mg terbinafine (base equivalent), the coat weight is about from about 0.5 or 1 to about 2 mg.

Typically, overall coating weights for coating materials vi) to vii) range from about 10 to about 200 % of core weight, preferably from about 50 to about 100 % of core weight.

Terbinafine base equivalent may be present in an amount of from about 0.1 to about 95 %, e.g. from about 20 to about 90 %, preferably from about 30 to about 80 %, especially from about 50 to about 60 % by weight based on the total weight of the composition.

The solid dosage forms typically may comprise **disintegrants**, e.g. such pharmaceutical excipients which facilitate the disintegration of a solid dosage form when placed in an aqueous environment, and may comprise e.g. the following:

(i) natural starches, such as maize starch, potato starch, and the like; directly compressible starches, e.g. Sta-rx^R 1500; modified starches, e.g. carboxymethyl starches and sodium starch glycolate, available as Primojel^R; Explotab^R; Explosol^R; and starch derivatives such as amylose;

(ii) crosslinked polyvinylpyrrolidones, e.g. crospovidones, e.g. Polyplasdone^R XL and

Kollidon^R CL;

(iii) alginic acid and sodium alginate;

(iv) methacrylic acid/divinylbenzene copolymer salts, e.g. Amberlite^R IRP-88; and

(v) cross-linked sodium carboxymethylcellulose, available as e.g. Ac-di-sol^R, Primellose^R, Pharmacel^R XL, Explocel^R and Nymcel^R ZSX.

Preferred disintegrants include those from classes (i) and (ii) above, particularly preferred are Starx^R, Primojel^R and Polyplasdone^R.

The disintegrant may be present in an amount of from about 1 to about 50 %, e.g. from about 5 to about 40 % by weight based on the total weight of the uncoated composition.

In a further aspect the invention provides a composition of the invention wherein the ratio of terbinafine (base equivalent) to disintegrant is from about 1 : 0.01 to about 1 : 20, e.g. from about 1 : 0.05 to about 1 : 5, preferably from about 1 : 0.05 to about 1 : 1 by weight.

The compositions of the invention may also comprise further components which are commonly employed in the preparation of dosage forms, e.g. solid dosage forms. These components include, among others: **binders; filler and plasticising agents; lubricants,** e.g. magnesium stearate; and **glidants**, e.g. silica, e.g. in particular colloidal silicon dioxide products available under the trademark Aerosil^R (see H.P. Fiedler, loc. cit. hereafter, p. 115; Handbook of Pharmaceutical Excipients, loc. cit. hereafter, p. 424).

Suitable **binders** include the following:

(i) starches, e.g. potato starch, wheat starch or corn starch;

(ii) gums such as gum tragacanth, acacia gum or gelatin;

(iii) microcrystalline cellulose, e.g. products known under the trademarks Avicel^R, Filtrak^R, Heweten^R or Pharmacell^R;

(iv) modified celluloses, e.g. hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropylmethyl cellulose, e.g. hydroxypropyl cellulose having a hydroxypropyl content of about 5 to 16 % by weight and of viscosity for 2 % w/w aqueous solutions of from about 2.0 to about 20 cps (= mPa.s), preferably from about 2.0 to about 6.0, e.g. 3.0 cps, e.g. hydroxypropyl methylcellulose (HPMC) (e.g. USP type 2910, 3 cps), available as e.g. Pharmacoat^R 603; and

(v) polyvinylpyrrolidone, available as e.g. Povidone^R, Kollidon^R or Plasdone^R.

A particularly preferred binder is HPMC (Pharmacoat^{R}). The binder may be present in an amount of from about 0.5 to about 50 %, e.g. from about 1 to about 40 %, e.g. from about 1 to about 25 %, e.g. from about 1 to about 15 %, preferably from about 1 to about 8 % by weight based on the total weight of the uncoated composition.

In a further aspect the invention provides a composition of the invention wherein the ratio of terbinafine (base equivalent) to binder is from about 1 : 0.01 to about 1 : 10, e.g. from about 1 : 0.01 to about 1 : 1, preferably from about 1 : 0.01 to about 1 : 0.1, especially about 1 : 0.04 by weight.

Suitable **filler and plasticising agents** include excipients known for their favourable properties as filler and plasticising agents, and include:

(i) substantially water-insoluble excipients such as microcrystalline cellulose (which may also be regarded as a weak disintegrant), e.g. Avicel^{R} , Pharmacel^{R}, Emcocell^{R}, Vivapurl^{R}, preferably Avicel^{R} (FMC Corp.), e.g. of the types Avicel^{R} PH101, 102, 105, RC 581 or RC 591 (Fiedler, loc.cit. hereafter, p. 216).

(ii) substantially water-soluble excipients such as compression sugars, e.g. lactose, sucrose, amylose, dextrose, mannitol and inositol, preferably lactose; and

(iii) calcium hydrogen orthophosphate dihydrate, e.g. Emcompress^{R}, or anhydrous calcium hydrogen phosphate, e.g. Fujicalin^{R}.

If present, the filler and plasticising agents may be present in an amount of from about 0.1 to about 50 %, e.g. from about 1 to about 40 %, preferably from about 5 to about 30 % by weight based on the total weight of the uncoated composition.

In a further aspect the invention provides a composition of the invention wherein the ratio of terbinafine (base equivalent) to filler or plasticising agent is from about 1 : 0.01 to about 1 : 100, e.g. from about 1 : 0.01 to about 1 : 20, preferably from about 1 : 0.01 to about 1 : 10, especially from about 1 : 0.1 to about 1 : 5, more especially about 1 : 0.2 by weight.

The compositions of the invention may conveniently further comprise a suitable **buffering component**, e.g. a salt of an acid that is partially dissociated in aqueous solution, and include those buffering components which - upon disintegration of the composition in an

aqueous medium (e.g. the oral cavity) - are capable of maintaining a pH at which terbinafine remains substantially insoluble, e.g. a pH in acidic range, e.g. a pH of greater than 4, preferably of from about 5 to about 6, on treatment with excess water, e.g. 5 to 100 ml. Examples of suitable buffers include carbonate, citrate, acetate, phosphate, phthalate, tartrate salts of the alkali and alkaline earth metal cations, such as sodium, potassium, magnesium and calcium. Preferred buffering agents include e.g. calcium carbonate, trisodium citrate and sodium hydrogen carbonate. The buffering agents may be used singly or in any suitable combination for achieving the desired pH and may be of a buffer strength of from about 0.01 to about 1 mole/litre, preferably from about 0.01 to about 0.1 mole/litre.

The molar ratio of terbinafine (base equivalent) to buffering component may be from about 1 : 0.02 to about 1 : 10, e.g. from about 1 : 0.2 to about 1 : 10, preferably from about 1 : 0.5 to about 1 : 5, more preferably from about 1 : 0.5 to about 1 : 2.

It will be appreciated that the invention encompasses:

a) in respect of the disintegrant any of components i) to v) individually or in combination with one or more of the other components i) to v);
b) in respect of the binder and filler or plasticizing agent any of those specified above individually or in combination; and
c) in respect of the buffering component any of the buffers specified above individually or in combination.

The compositions may conveniently also include one or more **further additives or ingredients** in an amount of e.g. from about 0.01 to about 5 % by weight based on the total weight of the uncoated composition, for example: **sweetening agents**, e.g. sorbitol, saccharin, aspartame, acesulfame or sugars such as glucose, fructose or saccharose; **flavouring agents**, e.g. chocolate, cocoa, banana, strawberry or vanilla flavour; and so forth. Additives to sugar or shellac coating commonly used in confectioning may be employed where appropriate.

Determination of workable proportions in any particular instance will generally be within the capability of the man skilled in the art. All indicated proportions and relative weight ranges described above are accordingly to be understood as being indicative of preferred or individually inventive teachings only and not as limiting the invention in its broadest aspect.

Especially **preferred compositions** of the invention are **coated minitablets or pellets wherein the coating comprises a** (taste-masking) **polyacrylate coating,** preferably Eudragit^R E or Eudragit RD100^R, especially Eudragit^R E, **whereby the polyacrylate coating and the terbinafine-containing core optionally are separated by a readily-dissolving** (protective) **coating** of, preferably, a cellulose derivative such as HPMC, and **optionally further coated with a layer preventing sticking** of the minitablets or pellets to each other or to the capsule shell, e.g. comprising colloidal silica such as Aerosil^R 200; most especially preferred are the compositions of **Examples 5, 8, 9 and 10**, preferably Examples 5 and 8, especially **Example 8.**

In a subgroup the (taste-masking) polyacrylate coating is separated from the core by a readily-dissolving (protective) coating as decribed above.

In yet another aspect the invention provides a **process for preparing a coated composition of the invention as defined above,** comprising **appropriately coating a corresponding uncoated precursor form of a composition of the invention,** using conventional methods, e.g. as described in Remington's Pharmaceutical Sciences, 18th Edition, Ed. Alfonso R. Gennaro, Easton, PA : Mack (1990); and in K. Bauer et al., Überzogene Arzneiformen (1988), Wissensch. VG, Stuttgart; the contents of which are incorporated herein. E.g. a coating system may be used in e.g. a conventional non-perforated pan or in a perforated pan by the Accela Cota method, or the submerged sword coating method or fluid bed coating method may be used.

The compositions of the invention thus obtained have an acceptable taste and thus have particularly good patient convenience and patient acceptance due to their increased ease of administration and ingestion. Furthermore, the compositions of the invention, preferably those that are in coated form, prevent taste disturbance or taste loss, probably by preventing terbinafine interference with taste receptors in the oral cavity, in particular on the tongue.

Thus, the compositions of the invention, which are conveniently in solid form, e.g. in the form of a coated tablet or of coated pellets or minitablets, or dragées (i.e. tablets coated with a coating containing sugar and/or sugar alcohols), preferably in the form of a coated tablet or coated minitablets or pellets, may be administered as such or, if desired, e.g. with coated

pellets or minitablets, dispersed (but preferably not substantially dissolved) prior to administration in a small amount of a liquid or semi-liquid, e.g. water, milk, yoghurt or juice, e.g. in a spoon.

In addition the compositions of the invention show surprisingly high physical and chemical stability, e.g. for up to two or more years. The physical and chemical stability may be tested in conventional manner, e.g. the compositions may be tested as such by measurement of dissolution, disintegration time, and/or by hardness test, e.g. after storage at room temperature, i.e. at 25°C, and/or after storage at 40°C. The taste of the compositions may be tested in standard clinical studies.

The particles of the multiparticulate system of the invention, e.g. minitablets or pellets may be packaged in conventional manner, e.g. in a bottle, or worked-up into optionally coloured capsules. Such capsules may be in e.g. two parts, and each part may conveniently be of a different colour.

The compositions of the invention are useful for the known indications of terbinafine, e.g. for the following conditions: onychomycosis caused by dermatophyte fungi, fungal sinusitis, tinea capitis, fungal infections of the skin, for the treatment of tinea corporis, tinea cruris, tinea pedis, and yeast infections of the skin caused by the genus Candida, e.g. Candida albicans, systemic mycosis, mycosis by azole-resistant strains, e.g. in combination with a 14-α-methyldimethylase inhibitor, or infections with Helicobacter pylori.

The compositions are particularly effective in treating **onychomycosis.**

In a further aspect of this embodiment the invention provides a **method of treatment of fungal infection** of the human body, e.g. onychomycosis, comprising **administering a pharmaceutically effective amount of a composition of the invention to a subject in need of such treatment.**

It further provides a **method of inhibiting or reducing taste disturbance or taste loss and associated adverse effects after terbinafine intake** which comprises **administering to a subject prone to taste disturbance or taste loss, a composition of the invention.**

It further provides the **use of a composition of the invention in the manufacture of a medicament** for the **treatment of fungal infections** of the human body, in particular of onychomycosis.

It further provides the **use of a composition of the invention in the manufacture of a medicament** for **inhibiting or reducing taste disturbance or taste loss and associated adverse effects** such as impaired appetite and weight loss **after terbinafine intake.**

It further provides the **use of a composition of the invention in the manufacture of a medicament** for **use in the method of the invention** as defined above.

The utility of the compositions of the invention may be observed in standard bioavailability tests or standard animal models, for example ascertaining dosages giving blood levels of terbinafine equivalent to blood levels giving a therapeutical effect on administration of known terbinafine oral dosage forms, e.g. a tablet. Typical doses are in the range of from about 1 mg/kg to about 10 mg/kg, e.g. from about 1.5 mg/kg to about 5 mg/kg, or e.g. from about 3 to about 4 mg/kg body weight of terbinafine base equivalent per day. The appropriate dosage will, of course, vary depending upon, for example, the host and the nature and severity of the condition being treated. However in general satisfactory results in animals are indicated to be obtained at daily treatments with doses from about 1 mg/kg to about 10 mg/kg animal body weight. In humans an indicated daily dosage is in the range of from about 10 mg to about 1000 mg per day, conveniently administered, for example, in divided doses up to four times a day or once daily. Preferred dosages for children weighing less than 20 kg may be about 62.5 mg once daily, for children weighing from 20 to 40 kg about 125 mg once daily, for children weighing more than 40 kg about 250 mg once daily, and for adults from about 250 mg to about 500 mg once daily.

Terbinafine may be administered in immediate release form, e.g. as a tablet or capsule, e.g. a tablet comprising 350 mg base equivalent of active substance, or e.g. one or two capsules with minitablets or pellets comprising 350 mg base equivalent of active substance in total, or in sustained release form. Immediate release forms are preferred.

Suitable sustained release forms are described in Pharmazeutische Technologie, Thieme Verlag, Stuttgart/New York, 2nd Edition [1991], Ed. H. Sucker, P. Fuchs, P. Spieser, e.g. on p. 370-390. Further systems are described in e.g. Pharmaceutical Dosage Forms, Ed. Herbert A. Lieberman, Leon Lachman, Joseph B. Schwartz, 2nd edition, Vol. 3, Marcel Dekker; and Remington, The Science and Practice of Pharmacy, Ed. Alfonso Gennaro, 19th Edition [1995]. A wide variety of sustained release systems may be used.

Details of excipients useful in compositions for use in the present invention are known, e.g. from the presently commercialized forms of Lamisil^R, or as described in **H.P. Fiedler**, "**Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete**", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded Edition (1996); or in "**Handbook of Pharmaceutical Excipients**", 2nd Edition, Ed. A. Wade and P.J. Weller (1994), Joint publication of American Pharmaceutical Association, Washington, USA and The Pharmaceutical Press, London, England; or may be obtained from brochures from the relevant manufacturers, the contents of which are hereby incorporated by reference.

The amount of terbinafine in a composition of the invention will of course vary, e.g. depending on to what extent other components are present. In general, however, the terbinafine will be present in an amount within the range of from 10 % to about 80 % by weight based on the total weight of the composition. Compositions will preferably be compounded in unit dosage form, e.g. by filling into capsule shells, e.g. soft or hard gelatin capsule shells or by tabletting or other moulding process. Thus unit dosage terbinafine composition, suitable for administration once or twice daily (e.g. depending on the particular purpose of therapy, the phase of therapy, etc.) will appropriately comprise half or the total daily dose contemplated. Preferably the compositions of the invention are administered once-a-day.

As indicated above, a preferred treatment method according to the invention (hereinafter referred to as **method A**) is an intermittent cycle wherein the terbinafine (350 mg base equivalent) is administered daily for about half, i.e. two weeks, of a 28 days or monthly cycle, followed by about 2 weeks, i.e. 14 or 16-17 days of rest (no drug). This cycle is then repeated for a total of three or four, especially three cycles.

The pharmacokinetic properties of the compositions of the invention may be determined in standard animal and human pharmacological (bioavailability) trials.

For example one standard pharmacological trial may be carried out in healthy male or female non-smoking volunteers aged between 18 to 45 years having within 20 % of the ideal body weight. Blood samples are taken for 1, 2, 4, 8, 16, 32 and 72 hours post-administration in the method of the invention and tested for terbinafine. Terbinafine blood plasma concentrations may be determined in conventional manner, e.g. by HPLC or GLC analytical techniques. Safety is judged according to a standard checklist based on Adverse Event symptoms after 1 week.

A further standard pharmacological trial is e.g. a bioavailability/food-effect study in a randomized, open-label , three-period, crossover study to evaluate the relative bioavailability of a composition of the invention, e.g. the capsules of Example 5 or 8, compared with standard terbinafine immediate release tablets and to assess the effect of food on the pharmacokinetics of the compositions of the invention after a single dose in 24 healthy adult subjects. The study includes the following three treatments:

- treatment A: 250 mg single standard immediate release tablet under fasted conditions;
- treatment B: 350 mg capsule (2 x 175 mg) of Example 5 under fasted conditions; and
- treatment C: 350 mg capsule (2 x 175 mg) of Example 5 under fed conditions.

For each of the three treatment periods, safety assessments are performed and blood samples collected at defined timepoints until 96 h post-dosing to determine i.a. terbinafine t_{max}, C_{max} and AUC (area under the curve).

Pharmacokinetic drug skin and nail concentration studies may be carried out according to the same principles as set out for the above-mentioned standard pharmacological trials. For example a clinical trial may be effected in Method A.

A therapeutic clinical trial may be effected based on the principles of the standard pharmacological trials mentioned above. For example, a randomized double-blind positive-controlled and placebo-controlled study may be effected with subjects having onychomycosis of the toe-nail confirmed by microscopy and culture. Treatment is carried out preferably with three 28-days or monthly cycles in the method of the invention, using the

175 mg capsules of Example 5, and with the original treatment over 12 weeks. Clinical trials may be effected in several hundred patients to ascertain the freedom from Adverse Events. However therapeutic efficacy may be shown in trials with 25 patients aged over 12 years. Safety is evaluated by an Adverse Event report of clinical aspects and vital signs. Efficacy is determined by microscopy, culture procedures and visually looking at signs and symptoms. Efficacy is seen in patients with the fungi described above, especially Trichophyton rubrum, Trichophyton mentagrophytes and Epidermophyton floccosum. Patients include those with predisposing factors such as impaired blood circulation, peripheral neuropathy, diabetes mellitus, damage from repeated minor trauma, and limited immune defects as well as AIDS. Patients have (i) distal lateral subungual onychomycosis starting at the hyponychium spreading proximally to the nail bed and matrix, (ii) proximal subungual onychomycosis, wherein the fungus infects the cuticle and eponychium to reach the matrix where it becomes enclosed into the nail plate substance, (iii) total dystrophic onychomycosis, and (iv) superficial white onychomycosis. If desired serum concentrations of terbinafine may be evaluated in conventional manner. Concentrations of terbinafine in the nail may be evaluated by both photo-acoustic spectroscopy and nail clipping followed by analysis, indicating presence of terbinafine in the nail-bed.

Clinical trials may be effected in particular sub-sets of subjects, e.g. those with impaired renal or hepatic function. Changes in the standard clinical chemistry parameters measured for liver dysfunction are lower than expected for the method of the invention. It is also found that any such dysfunctions are transient and functional. This indicates the excellent tolerability of the compositions of the invention.

The compositions for use in the method of the invention are useful for the same indications as for known immediate release terbinafine tablets, e.g. fungal sinusitis and onychomycosis. The utility of compositions of the invention may be observed in standard clinical tests or standard animal models.

The compositions in the method of the invention are particularly and surprisingly well tolerated with regard to the Adverse Events mentioned above, provoking fewer Adverse Events than would be expected in the original treatment with the standard 250 mg immediate release Lamisil^{R} tablet. From the clinical trials it is seen that the compositions of the invention

are just as efficacious particularly in aged patients, e.g. of 70 years and above, in patients with renal impairment (e.g. creatinine clearance ≥ 50 ml/min) or hepatic cirrhosis, and yet tend to provoke surprisingly fewer Adverse Events than expected for the dose given. Moreover the variation in AUC between fasted and fed state is less than expected.

The following Examples illustrate the invention. They are not limitative. All temperatures are in degrees Centigrade. The following abbreviations are used:

HPMC = hydroxypropylmethylcellulose
MW = molecular weight
PEG = polyethyleneglycol

Example A: Uncoated immediate release tablets

Tablets (immediate release) are made containing 350 mg terbinafine (base equivalent) in hydrochloride salt form in analogous manner to known Lamisil^{R} or other terbinafine tablets.

The tablets have the same composition as indicated under "Core" in Example 1 hereunder, and are without coating.

For use in the present invention for intermittent cycling, e.g. 1 tablet (350 mg) or 2 tablets (700 mg) are administered once a day for 14 consecutive days of each cycle.

Example B: Uncoated sustained-release tablets

Components	Amounts (mg/tablet)
Terbinafine hydrochloride*	393.75 mg
HPMC (Methocel^{R} K100MP)	51.75 mg
Microcrystalline cellulose	101.25 mg
Colloidal silica (Aerosil 200^{R})	2.73 mg
Magnesium stearate	2.73 mg
Total weight (of tablet)	552.21 mg

* corresponds to 350 mg terbinafine base

The formulation is prepared by conventional procedures. Terbinafine hydrochloride may be pre-granulated with e.g. one third of the hydroxypropyl methylcellulose.

For use in the present invention for intermittent cycling, e.g. 1 tablet (350 mg terbinafine base equivalent) or 2 tablets (700 mg) are administered once a day for 14 consecutive days of each cycle.

Example 1: Coated tablets

Coated tablets are prepared in conventional manner by aqueous granulation of a part of the ingredients, mixing with the other ingredients at dry stage, compressing and coating the resultant tablets with an aqueous dispersion of the coating ingredients. The tablets obtained have the following composition:

Components	Amounts	
	%	mg/tablet
Core:		
Terbinafine hydrochloride*	72.1	393.75
HPMC (USP type 2910, 3 cps)	3.0	16.38
Microcrystalline cellulose	12.4	67.62
Sodium starch glycolate	11.5	62.79
Colloidal silica	0.5	2.73
Magnesium stearate	0.5	2.73
Total weight (of uncoated tablet)	100.0	546.00
Coating:		
Eudragit E PO^{R} (powder)	68.5	4.00
Sodium dodecyl sulfate	4.5	0.26
Dibutyl sebacate	9.1	0.53
Magnesium stearate	18.0	1.05
Total weight (of coating per tablet)	100.0	5.84
Total weight (of coated tablet)		551.84

*corresponds to 350 mg terbinafine base

For use in the present invention for intermittent cycling, e.g. 1 tablet (350 mg terbinafine base equivalent) or 2 tablets (700 mg) are administered once a day for 14 consecutive days of each cycle.

Example 2 to 4: Coated minitablets

Minitablets are prepared in conventional manner by aqueous granulation of a part of the ingredients, mixing with the other ingredients at dry stage, compressing and coating the resultant minitablets with an aqueous dispersion of the coating ingredients. The resultant biconvex round minitablets have a diameter of about 2.0 to 2.1 mm:

Components	Example 2		Example 3		Example 4	
	% of total mass	mg/mini-tablet	% of total mass	mg/mini-tablet	% of total mass	mg/mini-tablet
Core:						
Terbinafine hydrochloride*	63.80	4.6875	64.17	4.6875	63.42	4.6875
HPMC 603 (USP type 2910, 3 cps)	2.65	0.1950	2.67	0.1950	2.64	0.1950
Microcrystalline cellulose	10.96	0.8050	11.02	0.8050	10.89	0.8050
Sodium carboxymethyl starch	10.17	0.7475	10.23	0.7475	10.11	0.7475
Colloidal silica	0.44	0.0325	0.44	0.0325	0.44	0.0325
Magnesium stearate	0.89	0.0653	0.89	0.0653	0.88	0.0653
Total weight (of uncoated minitablet)		6.5328		6.5328		6.5328
Coating 1:						
HPMC 603 (USP type 2910, 3 cps)	2.14	0.1570	2.15	0.1570	2.26	0.1671
PEG (nominal MW 8000)	0.43	0.0314	0.43	0.0314	0.45	0.0334
Silicic acid (Syloid 244FP)	1.71	0.1256	1.72	0.1256	1.80	0.1331
Coating 2:						
Eudragit E PO^{R} (powder)	4.27	0.3140	4.30	0.3140	4.52	0.3342
Sodium dodecyl sulfate	0.28	0.0206	0.28	0.0206	0.30	0.0220
Dibutyl sebacate	0.56	0.0413	0.57	0.0413	0.60	0.0440
Magnesium stearate	1.12	0.0825	1.13	0.0825	1.19	0.0880
Coating 3:						
Colloidal silica	0.57	0.0417	-	-	0.49	0.0363
Total weight (of coatings per minitablet)		0.8141		0.7724		0.8581
Total weight (of coated minitablet)	100	7.3469	100	7.3052	100	7.3909

*corresponds to 4.1667 mg terbinafine base

For use in the present invention for intermittent cycling, e.g. 84 minitablets (350 mg terbinafine base equivalent) are administered once a day for 14 consecutive days of each cycle.

Example 5: Hard gelatin capsules comprising doubly-coated minitablets with an anti-sticking layer

a) Minitablets:

Minitablets are prepared in conventional manner by aqueous granulation of a part of the ingredients, mixing with the other ingredients at dry stage, compressing and coating the resultant minitablets with an aqueous dispersion of the coating ingredients. The resultant biconvex round minitablets have a diameter of about 2.0 to 2.1 mm:

Components	Amount (mg/minitablet)
Inner phase:	
Terbinafine hydrochloride*	4.6875
HPMC 603 (USP type 2910, 3 cps)	0.1950
Microcrystalline cellulose	0.3325
Sodium carboxymethyl starch	0.5850
Colloidal silica (Aerosil 200^{R})	0.0325
Outer phase:	
Microcrystalline cellulose	0.4725
Sodium carboxymethyl starch	0.1625
Magnesium stearate	0.0653
Coating 1 (protecting):	
HPMC 603 (USP type 2910, 3 cps)	0.10026
PEG (nominal MW 8000)	0.02004
Colloidal silica (Aerosil 200^{R})	0.07986
Purified water**	2.03340
Coating 2 (taste-masking):	
Eudragit E PO^{R} (powder)	0.33420
Sodium lauryl sulfate	0.02200
Dibutyl sebacate	0.04400
Magnesium stearate	0.08800
Purified water**	1.60380
Anti-sticking layer:	
Colloidal silica (Aerosil 200^{R})	0.03625
Total weight (of coated minitablet)	7.25741

* corresponds to 4.1667 mg terbinafine base

**removed during manufacturing process

b) Capsules:

Coated minitablets obtained as described under a) above are filled into optionally coloured hard gelatin capsules in conventional manner.

For use in the present invention for intermittent cycling, e.g. one capsule containing 84 minitablets (1 x 350 mg) or two capsules containing 42 minitablets each (2 x 175 mg) (350 mg terbinafine base equivalent in total) is administered once a day for 14 consecutive days of each cycle.

Example 6: Hard gelatin capsules comprising uncoated minitablets

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, but omitting the two coatings and the anti-sticking layer (total weight: 6.5328 mg/minitablet).

Example 7: Hard gelatin capsules comprising mono-coated minitablets

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, but using for coating 1, 0.02662 mg colloidal silica (Aerosil 200^{R}) in place of 0.07986 mg and omitting coating 2 and the anti-sticking layer (total weight: 6.6797 mg/minitablet).

Example 8: Hard gelatin capsules comprising minitablets with reduced protecting coating

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, but using for coating 1, 0.02662 mg colloidal silica (Aerosil 200^{R}) in place of 0.07986 mg
(total weight: 7.20417 mg/minitablet).

Examples 9 and 10: Hard gelatin capsules comprising minitablets coated for taste-masking but devoid of protecting coating

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, except that the minitablets prepared are devoid of protecting coating 1 (total weight 7.05725 mg/minitablet) (**Example 9**); in a variant, they are devoid of protecting coating 1, and taste-masking coating 2 is devoid of Eudragit E^R, sodium lauryl sulfate and dibutyl sebacate and has the following composition:

Example 10	Amount (mg/minitablet)
Coating 2 (taste-masking):	
Magnesium stearate	0.06684
Polysorbate 80^R	0.06684
Eudragit RD100^R	0.33420
Purified water*	2.20572
Total weight (of coated minitablet)	7.03693

* removed during manufacturing process

Example 11: Hard gelatin capsules comprising minitablets with enhanced protecting coating

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, but for coating 1 (protecting) the amounts of HPMC and PEG 8000 are trebled (0.30078 and 0.06012 mg/minitablet, respectively), and 6.10020 mg purified water (removed during manufacturing process) is used in place of 2.03340 mg (total weight 7.49801 mg/minitablet).

Examples 12 to 14: Hard gelatin capsules comprising minitablets with modified coating 2

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, but for coating 1 (protecting) the amount of colloidal silica (Aerosil 200^R) is reduced (0.02662 mg/minitablet in place of 0.07986 mg/minitablet) and for coating 2 (taste-masking) the following ingredients are used:

Component	Amount (mg/minitablet) Example 12	Example 13	Example 14
Coating 2 (taste-masking):			
Eudragit E PO^R (powder)	0.3342	0.3342	0.3342
Sodium lauryl sulfate	0.03342	none	none
Dibutyl sebacate	none	none	0.01671
Magnesium stearate	0.11726	0.16710	0.16710
Stearic acid	0.04749	none	none
PEG 8000^R	none	0.03342	0.03342
Ethanol	none	2.88749	2.87746
Purified water*	3.03360	1.92499	1.91831
Total weight (coated minitablet)	7.24834	7.25069	7.26740

* removed during manufacturing process

Examples 15 and 16: Hard gelatin capsules comprising minitablets with modified antisticking layer

Minitablets are prepared and formulated into capsules and may be used for intermittent cycling as described in Example 5, but using for coating 1 (protecting) 0.02662 mg colloidal silica (Aerosil 200^R) in place of 0.07986 mg, and for the anti-sticking layer, replacing most (Example 15) or all (Example 16) of the colloidal silica with the following ingredients:

Component	Amount (mg/minitablet) Example 15	Example 16
Anti-sticking layer:		
HPMC 603^R	0.05013	none
PEG 8000^R	0.01002	0.07350
Colloidal silica (Aerosil 200^R)	0.01331	none
Purified water*	1.01670	0.66150
Total weight (of coated minitablet)	7.24138	7.24142

* removed during manufacturing process

Example 17: Coated pellets

Coated pellets are prepared in conventional manner by aqueous granulation of the pellet components, extrusion of the wet granulate, spheronization, drying and coating with an aqueous dispersion of the coating components. The resultant pellets have a particle size between about 0.8 and 1.0 mm and have the following composition:

Components	Amount (g/100 g coated pellets)
Core:	
Terbinafine hydrochloride*	42.591
Fujicalin^R	31.517
Microcrystalline cellulose	8.518
Sodium carboxymethyl starch	2.555
Purified water**	46.850
Coating (taste-masking):	
Eudragit E PO^R (powder)	8.518
Sodium lauryl sulfate	0.608
Dibutyl sebacate	1.272
Magnesium stearate	3.429
Purified water**	41.485
Anti-sticking layer:	
Colloidal silica (Aerosil 200^R)	0.990
Total weight (of coated pellets)	100.00

* corresponds to 37.859 mg terbinafine base per 100 g coated pellets
**removed during manufacturing process

For use in the present invention for intermittent cycling, e.g. 924.5 mg coated pellets (350 mg terbinafine base equivalent) are administered once a day for 14 consecutive days of each cycle.

Example 18: Hard gelatin capsules comprising coated pellets

Coated pellets obtained as described in Example 17 above are filled into optionally coloured hard gelatin capsules in conventional manner.

For use in the present invention for intermittent cycling, e.g. two capsules containing 462.25 mg coated pellets each (2 x 175 mg terbinafine base equivalent) or three capsules containing 308.16 mg coated pellets each (3 x 116.67 mg terbinafine base equivalent) (350 mg terbinafine base equivalent in total) are administered once a day for 14 consecutive days of each cycle.

Claims:

1. A terbinafine solid **dosage form** for oral administration which is coated and/or is multiparticulate.
2. A dosage form of claim 1 which comprises coated tablets.
3. A dosage form of claim 1 which is multiparticulate.
4. A dosage form of claim 1 which comprises optionally coated minitablets or pellets, preferably in capsules.
5. A dosage form of claim 1 which is adapted for release of the active substance terbinafine in the stomach.
6. A dosage form of claim 5 in which terbinafine is released and dissolves within 30 minutes to the extent of at least 50 % in 0.04 M citrate buffer pH 3.0 at 37°C.
7. A dosage form of claim 1 which has taste-masking properties and/or prevents taste disturbance or taste loss and associated adverse effects.
8. A dosage form of claim 1 which comprises coated minitablets or pellets wherein the coating comprises a polyacrylate coating, whereby the polyacrylate coating and the terbinafine-containing core optionally are separated by a readily-dissolving coating, and optionally further coated with a layer preventing sticking.
9. A dosage form of claim 8 wherein the polyacrylate is Eudragit^{R} E.
10. A dosage form of claim 8 wherein the readily-dissolving coating comprises a cellulose derivative.
11. A dosage form of claim 8 wherein the layer preventing sticking comprises colloidal silica.
12. A dosage form of claim 8 which is the minitablets in hard gelatin capsules of Example 8.

13. A **process** for preparing a dosage form of claim 1 which is coated, comprising appropriately coating a corresponding uncoated precursor form thereof.
14. **Use** of a dosage form of claim 1 in the manufacture of a medicament for the treatment of fungal infection of the human body, in particular of onychomycosis.
15. **Use** of a dosage form of claim 1 in the manufacture of a medicament for inhibiting or reducing taste disturbance or taste loss and associated adverse effects after terbinafine intake.

16. A **method** of inhibiting or reducing taste disturbance or taste loss and associated adverse effects after terbinafine intake which comprises administering to a subject prone to taste disturbance or taste loss, a dosage form of claim 1.
17. A **method** of treatment of fungal infection comprising administering to a subject in need of such treatment a pharmaceutically effective amount of a dosage form of claim 1.

18. A **method** of administering terbinafine to a subject in need of terbinafine treatment which comprises administering to the subject terbinafine in an intermittent cycle wherein the terbinafine is administered for more than one-third of the cycle.
19. The method of claim 18 wherein terbinafine is administered for about one-half of the cycle.
20. The method of claim 18 wherein there are 3 or 4 cycles.
21. The method of claim 18 wherein a cycle is a 28 days or a calendar month.
22. The method of claim 18 wherein the terbinafine is administered in three 28 days or monthly cycles of once daily oral administration of 350 mg/day (base equivalent) for 14 consecutive days of each cycle.
23. The method of claim 18 wherein the subject is suffering from onychomycosis.
24. The method of any one of claims 18 to 23 wherein terbinafine is administered as a dosage form of claim 1.

25. **Use** of terbinafine as an active agent in the manufacture of a medicament for use in the method of any one of claims 18 to 23.

26. **Use** of a dosage form of claim 1 in the manufacture of a medicament for use in the method of any one of claims 18 to 23.

27. A **pack** containing a plurality of terbinafine compositions arranged to be dispensed in the method of any one of claims 18 to 23, where convenient together with instructions for use, such as a calendar pack.