

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 June 2011 (03.06.2011)

PCT

(10) International Publication Number
WO 2011/064558 A2

(51) International Patent Classification:
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/GB2010/002199

(22) International Filing Date:
30 November 2010 (30.11.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2766/MUM/2009 30 November 2009 (30.11.2009) IN

(71) Applicant (for all designated States except US): **CIPLA LIMITED**; Mumbai Central, Mumbai 400 008 (IN).

(71) Applicant (for MW only): **CURTIS, Philip, Anthony** [GB/GB]; A.A. Thornton & Co., 235 High Holborn, London WC1V 7LE (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LULLA, Amar** [IN/IN]; 131 Maker Towers "L", 13th Floor, Cuffe Parade, Colaba, Mumbai 400 005, Maharashtra (IN). **MALHOTRA, Geena** [IN/IN]; 4 Anderson House, Opposite Mazgaon Post Office, Mazgaon, Mumbai 400 010, Maharashtra (IN).

(74) Agent: **CURTIS, Philip, Anthony**; A.A. Thornton & Co, 235 High Holborn, London WC1V 7LE (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: PHARMACEUTICAL COMPOSITION

(57) Abstract: The invention relates to a pharmaceutical composition comprising liposomes and at least one pharmaceutically acceptable excipient, wherein the liposomes comprise a lipid core containing voriconazole. The invention also relates to a method of making pharmaceutical compositions and to their use as a medicament.



WO 2011/064558 A2

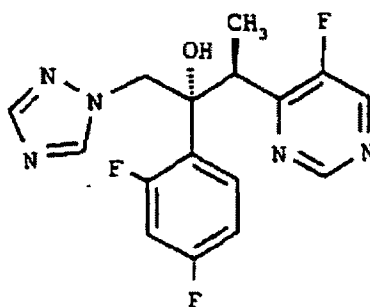
Pharmaceutical Composition

Field of the Invention

The present invention relates to a pharmaceutical composition of voriconazole, in particular
5 the present invention relates to a pharmaceutical composition of voriconazole in the form of
ready to use for prevention or treatment of topical or systemic infections and also therapeutic
and prophylactic use of the said composition.

Background and Prior art

- 10 Voriconazole is disclosed in European Patent Application 0440372 and has the scientific
name- (2R,3S)-2-(2,4-Difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-
butan-2-ol. It has the following structure:



- Voriconazole is useful in the treatment of fungal infections. Dosage forms of voriconazole
15 approved in the US are lyophilized powder for solution for intravenous infusion, film-coated
tablets for oral administration, and as a powder for oral suspension.

Voriconazole has a low aqueous solubility (0.2 mg/ml at pH 3), and is not stable in water (an
inactive enantiomer is formed from recombination of the retro-aldol products of hydrolysis).

- 20 Degradation of voriconazole occurs in aqueous solution, particularly under basic conditions.

- Thus, development of an aqueous intravenous formulation with a sufficient shelf life is
difficult. These problems are magnified by the semi-polar nature of the compound (log
D=1.8) which means that it is not generally solubilized by conventional means such as oils,
25 surfactants or water miscible co-solvents.

Accordingly various attempts have been made in the prior art to develop a formulation of voriconazole that increases its solubility and aqueous stability.

Any discussion of the prior art throughout the specification should in no way be considered
5 as an admission that such prior art is widely known or forms part of common general knowledge in the field.

US5116844 discloses novel triazole derivatives such as voriconazole, which have antifungal activity and are useful in the treatment of fungal infections in animals, including humans.

10

WO98/58677 discloses that the solubility of voriconazole in water can be increased by molecular encapsulation with sulphoalkylether cyclodextrin derivatives of the type disclosed in WO91/11172, particularly beta-cyclodextrin derivatives wherein the cyclodextrin ring is substituted by sulphobutyl groups. However, the cyclodextrin encapsulated voriconazole may
15 not remain stable when developed into aqueous ready to use compositions. Moreover, there are complex manufacturing issues associated with cyclodextrin formulations and that also increases manufacturing cost significantly.

WO97/28169 (see Examples 3-5) discloses a phosphate pro-drug of voriconazole, which
20 exhibits increased solubility and aqueous stability. However, the pro-drug may not exhibit 100% bioequivalence to voriconazole, and also the cost of manufacturing is again significantly increased.

US2005112204 discloses a pharmaceutical formulation of voriconazole, in particular an
25 aqueous micellar poloxamer preparation comprising voriconazole, and one or more poloxamer. However, still there is likelihood of degradation of voriconazole due to intimate contact with water and thus may be prone to result in unstable formulation.

US6632803 discloses a pharmaceutical formulation comprising voriconazole, or a
30 pharmaceutically acceptable derivative thereof, and a sulfobutylether beta-cyclodextrin.

WO 2004/032902 discloses compositions of an aqueous suspension of submicron- to micron-size particles of an antifungal agent (triazole antifungal agent such as itraconazole, ketoconazole, miconazole, fluconazole, ravuconazole, voriconazole, saperconazole, eberconazole, genaconazole, and posaconazole) coated with one or more surfactants. The
5 particles of the antifungal agent should have a volume-weighted mean particle size of less than about 50 microns in diameter.

Dale et al (Titled "Liposome ocular delivery systems", Advanced Drug Delivery Reviews, 16, 1995; 75-93) discloses liposomes as a means of delivering drugs to ocular cavity, and
10 methods of encapsulation of liposomes.

Thus, in the prior art there is not much disclosure about how to formulate a stable voriconazole ready to use composition.

15 Hence there still exists a need to develop pharmaceutical compositions of voriconazole having improved aqueous stability over the storage period when formulated in the form of ready to use aqueous composition.

Object of the invention

20

The object of the present invention is to provide a ready to use pharmaceutical composition of voriconazole having improved aqueous stability.

Another object of the present invention is to provide a process of manufacturing said
25 pharmaceutical composition.

Yet another object of the present invention is to provide method of preventing or treating the topical or systemic infections using said pharmaceutical composition.

30 **Summary of the invention**

According to one aspect of the present invention there is provided a pharmaceutical composition comprising voriconazole encapsulated lipid cores in the form of liposomes and optionally one pharmaceutically acceptable excipient.

- 5 According to another aspect of the present invention there is provided a process of manufacturing voriconazole encapsulated lipid cores.

According to a further aspect of the present invention there is provided a process of manufacturing the pharmaceutical composition comprising voriconazole encapsulated lipid
10 cores.

According to another aspect of the present invention there is provided a method of improving the aqueous stability of the voriconazole by encapsulating the voriconazole in lipid cores.

- 15 According to another aspect of the present invention there is provided use of a pharmaceutical composition comprising voriconazole encapsulated lipid cores in the manufacture of a medicament for treating topical or systemic fungal infection in patients in need thereof.

- 20 According to another aspect of the present invention there is provided a method of preventing or treating the topical or systemic infections comprising administering the pharmaceutical composition comprising voriconazole encapsulated lipid cores to a patient in need thereof.

Detailed Description

25

As discussed above, there is a need to develop a pharmaceutical composition of voriconazole having improved aqueous stability when formulated in the form of ready to use aqueous compositions.

- 30 The present inventors now, surprisingly, have found that when voriconazole encapsulated lipid cores are used to formulate the voriconazole aqueous compositions, the aqueous

stability of the compositions was significantly improved and such compositions may also be able to deliver effective amounts of voriconazole over the treatment period.

The present invention provides voriconazole encapsulated lipid cores. Particularly, the present invention provides a pharmaceutical composition comprising voriconazole encapsulated lipid cores in the form of liposomes, a vehicle and at least one pharmaceutically acceptable excipient.

The terms "voriconazole" is used throughout the description in broad sense to include not only the voriconazole *per se* but also their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs. Pharmaceutically acceptable salts of voriconazole include the acid addition and base salts thereof.

The term "voriconazole encapsulated in lipid cores" as used throughout the description is used in the broad sense to include voriconazole molecules partially or completely coated with lipid layer and/or voriconazole molecules entrapped between the lipid layers.

The present invention also provides a method of improving the aqueous stability of the voriconazole by encapsulating voriconazole in lipid cores

According to the present invention, the liposomes may be prepared using various phospholipids or lipid components, particularly lipids used for production of liposome vesicles/cores may be selected from those known to a person skilled in the art like natural phospholipids such as egg yolk lecithin (phosphatidylcholine), soybean lecithin, cholesterol, lysolecithin, sphingomyelin, phosphatidic acid, phosphatidylserine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, diphosphatidylglycerol, cardiolipin, plasmalogen, etc., or hydrogenation products obtainable from said phospholipids by the conventional technology (Hydrogenated soy phosphatidylcholine), and synthetic phospholipids such as dicetyl phosphate,

distearoylphosphatidylcholine, dipalmitoylphosphatidylcholine, dipalmitoylphosphatidyl glycerol, distearoylphosphatidyl glycerol, dilaurylphosphatidylglycerol, dipalmitoylphosphatidylethanolamine, dipalmitoylphosphatidylserine, eleostearoylphosphatidylcholine, eleostearoylphosphatidylethanolamine, 5 eleostearoylphosphatidylserine, dipalmitoylphosphatidyl acid, dipalmitoylphosphatidyl ethanolamine, their salts and the corresponding distearoyl- and dimyristyl- counterparts and/or mixtures thereof. The ratio of drug to lipid in the liposomal composition according to the present invention may range from 1:1 to 1:15.

10 The lipids or their mixtures may further contain suitable agents selected from dicetylphosphate, cholesterol, coprostanol, cholestanol, cholestane, ergosterol, phytosterol, sitosterol, lanosterol, protein (e.g. albumin, immunoglobulin, casein, insulin, hemoglobin, lysozyme, immunoglobulin, [alpha]-2-macroglobulin, fibronectin, vitronectin, fibrinogen, lipase, or enzyme) which strengthens the lipid, α -tocopherol, stearic acid, deferoxime 15 mesylate, stearyl amine and/or mixtures thereof.

The pharmaceutical composition of the present invention may further comprise suitable lipid carriers such as but not limited to hydrogenated egg phosphatidylcholine, hydrogenated soya lecithin, hydrogenated soya phosphatidylcholine and distearoyl or dipalmitoyl 20 phosphatidylcholine, surfactants, solvents.

Suitable free radical scavengers may also be used to control the lipid oxidation or peroxidation damage, particularly when the liposome composition is stored over an extended period at a temperature above that of the refrigeration temperatures.. Examples of suitable 25 free radical scavengers include, but not limited to: α -tocopherol, BHT (butylhydroxytoluene), BHA (butylhydroxyanisole), , propyl gallate, ascorbic acid, and water soluble iron and calcium chelator such as ethylenediaminetetraacetic acid (EDTA), biethylenediaminepentaacetic acid (BTPA), and ED3A.

30 A suitable aqueous medium used for rehydration is, for example, water or water containing dissolved salts, saccharides or a buffer. Examples of such salts, saccharides or buffers may include sodium chloride, dextrose, lactose and phosphate buffered saline (PBS) and

equivalents. Other buffers that may be included include but are not limited to disodium succinate hexahydrate, borate, citrate, phosphate, acetate, physiological saline, Tris-HCl(Tris-(hydroxymethyl)-aminomethane hydrochloride), HEPES (N-2-hydroxyethyl piperazine-N1-2-ethane sulfonic acid), sodium phosphate, sodium borate, physiological
5 saline, citrate, carbonate, phosphate and/or mixtures thereof to achieve desired osmolarity.

The pharmaceutical composition of voriconazole according to the present invention may further comprise suitable pH adjusting agent(s) to adjust the pH of the composition, suitable for topical or parenteral administration. It will also be appreciated that pH of the
10 pharmaceutical composition of the present invention may be modified based on the route of administration, dosage delivery form and particular patient need. For example, the pH of the ophthalmic composition, for the purpose of the present invention may be adjusted between 5 to 7 and pH of the parenteral composition, for the purpose of the present invention may be adjusted between 3 to 9.

15

During preparation of the liposomes, organic solvents are used to solubilize the lipids and active ingredient. Suitable organic solvents selected are those with a variety of polarities and dielectric properties, which solubilize the lipids, and include but are not limited to halogenated, aliphatic, cycloaliphatic, or aromatic-aliphatic hydrocarbons, such as benzene,
20 chloroform, methylene chloride, or alcohols, such as methanol, ethanol, or dimethyl sulphoxide and/or mixtures thereof. As a result, solutions (mixtures in which the lipids and other components are uniformly distributed throughout) containing the lipids are formed. Solvents are generally chosen on the basis of their biocompatibility, low toxicity, and solubilization abilities. For the purposes of the instant invention, the organic solvent
25 chloroform and/or equivalents are preferred.

The present invention further provides a process of manufacturing the pharmaceutical composition comprising voriconazole encapsulated lipid cores, which process comprises:

- (1) Dissolving voriconazole, one or more lipid components, lipid carriers, and an antioxidant
30 in one or more organic solvent(s).
- (2) Drying/Evaporating the lipid solution to form a drug-lipid film.
- (3) Rehydrating the drug-lipid film with rehydrating solution..

(4) Reducing the vesicle size to desired size

The present invention further provides another process of manufacturing the pharmaceutical composition comprising voriconazole encapsulated lipid cores, which process comprises:

- 5 (1) Dissolving voriconazole, one or more lipid components, lipid core strengthening agents, and an antioxidant in one or more organic solvent(s).
(2) The mixture obtained in step (1) is injected into an aqueous solution containing the water soluble components that have been previously heated.
(3) The solvent was evaporated by heating so as to obtain the voriconazole loaded liposomes.

10

The pharmaceutical composition comprising voriconazole encapsulated lipid cores which is obtained by the above mentioned processes can then be used for formulating suitable dosage forms.

- 15 In a particularly preferred embodiment to make voriconazole encapsulated lipid cores, soya lecithin and optionally additional lipid components are dissolved with voriconazole in one or more organic solvent(s), which is preferably chloroform, ethanol, methylene chloride and dimethyl sulphoxide. In the resulting solution, antioxidants such as α -tocopherol, BHT (butylhydroxytoluene) and BHA (butylhydroxyanisole) and optionally additional lipids may
20 also be dissolved.

- Cholesterol or another sterol, such as ergosterol, stigmasterol, or androsterone, may be included to improve the stability of the resulting liposomes, and thus maintain the liposome intact during circulation in the bloodstream. The lipid solution may be subjected to solvent
25 evaporation by various techniques known to the person skilled in the art to form a drug-lipid film in the reaction vessel.

- The solvent of the lipid-drug mixture may be removed by any suitable known technique, such as evaporation in which the organic solvents are removed under vacuum by rotary
30 evaporation or by spray drying to obtain a dry powder of the drug-lipid mixture.

Further, rehydration of lipid-drug mixture may be done by addition of aqueous medium or buffer solution and mixed by any appropriate method including, but not limited to, sonicating or vortexing the mixture, thereby forming the initial liposomes (e.g., dispersion of unilamellar vesicles). The liposome dispersion is preferably formed in the absence of any organic solvents. The drug entrapped liposomes may also be formed by applying shearing force by sonication/ high pressure homogenization, extrusion, or by freezing and thawing, from lipids, or any other known methods used by a person skilled in the art.

Among the additional lipid components that may be dissolved in the voriconazole-soy-
lecithin solution, hydrogenated egg phosphatidylcholine, hydrogenated soy lecithin, hydrogenated soy phosphatidylcholine and distearoyl or dipalmitoyl phosphatidylcholine are preferable materials. Hydrogenated natural phospholipids or saturated aliphatic phospholipids are believed to work well because the lack of double bonds in the side chains is thought to render the liposomes resistant to oxidation and hence are more physically stable.

The organic solvents may be removed from the solution by rotary evaporation, for example in a round bottom flask, leaving a dry film comprised of the complex and other lipid materials. Other equivalent methods of solvent removal are also suitable, such as drying under vacuum. Alternatively, the solution can be applied to a spray dryer and solvent removed in a continuous process to produce large quantities of a free flowing white powder for liposome preparation.

It will be appreciated to the person skilled in the art that various methods of making the liposomes can be employed in formulating the liposomes for the purpose of the present invention, such as disclosed in U.S. Pat. Nos. 5,567,434, and many more which disclose methods of making liposome vesicles with enhanced entrapment capacity which are hereby incorporated by reference in its entirety.

The size of the liposomes can be controlled using a variety of known techniques but not limited to sonication, homogenization and extrusion.

The present invention is adaptable, in particular, to scaling up production of the small or large unilamellar liposomes. Such small liposomes may preferably be sterilized by filtration since their diameter is less than 0.2 micrometer. Preferably, more than 70% of the voriconazole becomes associated with the liposome fraction when this technique is
5 employed.

In one embodiment, the present invention may be formulated as a suitable ocular dosage form

10 The process for preparing the ocular dosage formulation, voriconazole encapsulated lipid cores obtained according to the present invention is further aseptically filtered.

To formulate the ocular dosage formulation, voriconazole encapsulated lipid cores obtained according to the present invention may be admixed with other suitable pharmaceutically
15 acceptable excipients such as charge inducers and other suitable pharmaceutically acceptable excipients required to formulate a ocular dosage form such as but not limited to preservatives, charge inducing agents, isotonicity adjusting agents, wetting agents.

Charge inducers are used to impart charge on the vesicles to increase its stability by
20 prevention fusion of vesicles and providing higher value of zeta potential and also increase the contact time with the cornea. Suitable positively charged inducers are stearylamine, cetyl pyridinium chloride and negatively charge inducers are lipoaminoacid and dicetyl phosphate

The ocular dosage form may be present, typically in the form of drops of solution in isotonic,
25 pH-adjusted, sterile saline.

Suitable preservatives which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, benzalkonium chloride, benzethonium chloride and cetyl pyridinium chloride, benzyl bromide, benzyl alcohol, disodium EDTA, phenylmercury
30 nitrate, phenylmercury acetate, thimerosal, merthiolate, acetate and phenylmercury borate, polymyxin B sulphate, chlorhexidine, methyl and propyl parabens, phenylethyl alcohol,

quaternary ammonium chloride, sodium benzoate, sodium propionate, stabilized oxychloro complex, and sorbic acid.

Examples of suitable polymers include, but are not limited to: cellulose derivatives such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose; polyvinylpyrrolidone and
5 polyvinylalcohol or mixtures thereof. Polymers are used to attend the desired viscosity of the composition.

Examples of suitable wetting agents include, but are not limited to: polyoxyethylene, sorbitan monolaurate and stearate.

10

Examples of isotonicity adjusting agents include, but are not limited to: sodium chloride, D-mannitol, glucose, and glycerol, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and various nitrates, citrates, acetates or their mixtures.

15 Examples of pH adjusting agents include, but are not limited to: sodium hydroxide, citric acid, hydrochloric acid, acetic acid, phosphoric acid, succinic acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide, magnesium oxide, calcium carbonate, magnesium carbonate, magnesium aluminum silicates, malic acid, potassium citrate, sodium citrate, sodium phosphate, lactic acid, gluconic acid, tartaric acid, 1,2,3,4-butane
20 tetracarboxylic acid, fumaric acid, diethanolamine, monoethanolamine, sodium carbonate, sodium bicarbonate, triethanolamine, or combinations thereof.

Examples of charge inducing agents include, but are not limited to: stearylamine, cetyl pyridinium chloride, lipoaminoacid and dicetyl phosphate or combinations thereof.

25

The liposomal composition according to the present invention further may contain additional one or more ophthalmic drugs suitable for delivery in liposomal-entrapped form, for sustained release over a several-hour period, including: antiviral agents, such as fluorouracil, iodouridine, trifluorouridine, vidarabine, azidothymidine, ribavirin, phosphonoformate,
30 phosphonoacetate, and acyclovir; anti-allergic agents such as cromolyn, cimetidine, naphazoline, lodoxamide, and phenylepinephrine; anti-inflammatory agents such as prednisolone, dexamethasone, and supraphen; and anti-glaucoma agents which act by lowering

intraocular pressure, such as carbachol, N-demethylcarbachol, pilocarpine, anti-glaucoma agents which act as cholinesterase inhibitors, such as isofluorophate, exothioiodate, and demecarium bromide, and anti-glaucoma agents which act as .beta.-blockers, such as timolol, depaxolol, meti-pranalol, levobunalol, and celiprolol.

5

The pharmaceutical composition according to the present invention may also be formulated for administration directly to the ear.

Other formulations suitable for ocular and aural administration include ointments, 10 biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes.

These formulations may comprise polymers such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, 15 hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

20 In another embodiment, the present invention may be formulated as a suitable parenteral dosage form.

The process for preparing the ocular dosage formulation, voriconazole encapsulated lipid cores obtained according to the present invention is further aseptically filtered.

25

Compositions of the present invention, suitable for parenteral administration, may be formulated by various methods known in the art. Preferably, an injectable solution is made up with saline to provide a solution which is iso-osmotic with blood. These formulations may be 30 sterilized after preparation. They can be provided in any suitable form and in any suitable containers appropriate to maintaining sterility. It is generally preferred that formulations of the present invention are provided in a form suitable for direct injection. It will be readily

appreciated by those skilled in the art how to administer formulations of the present invention to a human or animal.

The pharmaceutical composition of the present invention may also be administered directly
5 into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

10

Parenteral compositions are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), however, if necessary for some applications, the composition may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable
15 vehicle such as sterile, pyrogen-free water.

The preparation of parenteral compositions under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

20

Compositions for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted
25 depot providing modified release of the active agent.

The dose of pharmaceutical composition of the present invention may be tailored depending on the intensity of the infection and individual patient need. For example, EPA440372 describes a suitable dose for the parenteral administration of voriconazole. A typical dose is
30 between 0.1 to 25 mg/kg, such as 0.5 to 20 mg/kg, for example 1 to 10 mg/kg, administered twice a day.

The parenteral formulation comprising voriconazole encapsulated lipid cores obtained according to the present invention may then be admixed with other suitable pharmaceutically acceptable excipients used in parenteral dosage forms such as but not limited to preservatives.

5

Suitable preservatives which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, benzalkonium chloride, benzyl alcohol, chlorobutol, chlorobutanol phenol, chlorocresol, phenylmercuric salts, methyl hydroxyl benzoate, methyl paraben, propyl paraben and cetylpyridinium chloride.

10

In yet another embodiment, the present invention may be formulated as a suitable solid oral dosage form, including but not limited to tablets which may be coated and pellets in capsules but also other conventional dosages such as powders, pellets, capsules, soft gelatin capsules, suspensions, solutions, emulsions and sachets may be provided.

15

The tablet formulation may be prepared by adsorbing the voriconazole encapsulated lipid cores on suitable carrier and further admixing with other suitable pharmaceutically acceptable excipients such as disintegrants, diluents, binders, glidants, anti-adherants used in tablet dosage forms

20

The voriconazole encapsulated lipid cores that are adsorbed on suitable carriers may also be filled in hard gelatin capsules and further admixing with other suitable pharmaceutically acceptable excipients disintegrants, diluents, binders, glidants, anti-adherants used in capsule dosage forms.

25

The soft gelatin capsule may be prepared by filling the voriconazole encapsulated lipid cores in capsule shell.

Suitable disintegrating agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, hydroxypropyl cellulose (HPC), low density HPC, carboxymethylcellulose (CMC), sodium CMC, calcium CMC, croscarmellose sodium; starches exemplified under examples of fillers and also carboxymethyl starch,

30

hydroxypropyl starch, modified starch; crystalline cellulose, micro crystalline cellulose, sodium starch glycolate, alginic acid or a salt thereof, such as sodium alginate or their equivalents and mixtures thereof.

- 5 Suitable carriers, diluents or fillers or bulking agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, lactose (for example, spray-dried lactose, α -lactose, β -lactose) lactose available under the trade mark Tablettose, various grades of lactose available under the trade mark Pharmatose or other commercially available forms of lactose, lactitol, saccharose, sorbitol, mannitol, dextrates, 10 dextrans, dextrose, maltodextrin, croscarmellose sodium, microcrystalline cellulose (for example, microcrystalline cellulose available under the trade mark Avicel), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC), methylcellulose polymers (such as, for example, Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium 15 carboxymethylcellulose, carboxymethylene, carboxymethyl hydroxyethylcellulose and other cellulose derivatives, starches or modified starches (including potato starch, corn starch, maize starch and rice starch) and mixtures thereof.

- Suitable anti-adherents, lubricants and glidants which may be used in the pharmaceutical 20 composition of the present invention, include, but are not limited to, stearic acid and pharmaceutically acceptable salts or esters thereof (for example, magnesium stearate, calcium stearate, sodium stearyl fumarate or other metallic stearate), talc, waxes (for example, microcrystalline waxes) and glycerides, light mineral oil, PEG, silica acid or a derivative or salt thereof (for example, silicates, silicon dioxide, colloidal silicon dioxide and polymers 25 thereof, crospovidone, magnesium aluminosilicate and/ or magnesium aluminometasilicate), sucrose ester of fatty acids, hydrogenated vegetable oils (for example, hydrogenated castor oil), or mixtures thereof.

- Suitable binders which may be used in the pharmaceutical composition of the present 30 invention, include, but are not limited to polyvinyl pyrrolidone (also known as povidone), polyethylene glycol(s), acacia, alginic acid, agar, calcium carragenan, cellulose derivatives such as ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl

cellulose, sodium carboxymethylcellulose, dextrin, gelatin, gum arabic, guar gum, tragacanth, sodium alginate, or mixtures thereof or any other suitable binder.

Suitable chelating agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to ethylenediaminetetraacetic acid (EDTA), disodium EDTA and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, and sodium desoxycholate and derivatives thereof.

The oral dosage formulation, according to the present invention, may be enteric coated, seal coated and/or film coated.

Suitable seal coating materials which may be used in the pharmaceutical composition of the present invention, include, but are not limited to hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, hypromellose, acacia, gelatin to increase adherence and coherence of the seal coat.

Suitable enteric coating materials which may be used in the pharmaceutical composition of the present invention, include, but are not limited to EUDRAGIT L 30 D-55, EUDRAGIT L100-55, EUDRAGIT S 100, EASTACRYL 30D, KOLLICOAT MAE 30 DP, KOLLICOAT MAE 100 P; cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate and combinations thereof.

In one embodiment the pharmaceutical composition of the present invention can be formulated in a suitable liquid oral dosage form, including but not limited to emulsions, solutions, suspensions, syrups, and elixirs.

The oral dosage formulation may be prepared by admixing voriconazole encapsulated lipid cores obtained according to the present invention with other suitable pharmaceutically acceptable excipients such as sweeteners, vehicle/wetting agents, coloring agents, flavoring agents, preservatives, viscosity enhancing/thickening agents.

Suitable viscosity enhancing/thickening agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, methylcellulose,

hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxy ethyl propyl cellulose, starches (such as maize or corn starch, potato starch, rice starch, tapioca starch, and wheat starch), carboxyvinyl polymers (carbomers such as Carbopol®), carboxymethyl cellulose and salts thereof, microcrystalline cellulose and arabic gum, guar gum, and xanthan gum, and mixtures thereof..

Suitable vehicle/wetting agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to glycerol, propylene glycol, liquid polyethylene glycols, sorbitol and mixtures thereof.

Suitable flavouring agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to cherry, raspberry, pineapple, black currant, strawberry flavour, caramel chocolate flavour, mint cool flavour, fantasy flavour, meat flavours and the like.

Suitable sweeteners which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, saccharin, aspartame, acesulfame, cyclamate, alitame, a dihydrochalcone sweetener, monellin, neohesperidin, neotame, stevioside and sucralose, the pharmaceutically acceptable salts and mixtures thereof.

Suitable colouring agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to quinoline yellow.

Suitable preservatives which may be used in the pharmaceutical composition of the present invention, include, but are not limited to, sodium benzoate, benzoic acid, potassium sorbate, sorbic acid, methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate, sodium methyl p-hydroxybenzoate, sodium ethyl p-hydroxybenzoate, sodium propyl p-hydroxybenzoate, sodium butyl p-hydroxybenzoate, domiphen bromide, sodium propionate, propylene glycol and mixtures thereof.

Alternatively, the voriconazole liposome dispersion of the present invention may be processed by one or more cycles of freezing and thawing (e.g.; to form a suspension of multilamellar vesicles). For example, two to five repeated cycles of freezing and thawing can

be advantageously used to form the suspension. Following the freeze-thaw cycle(s), the liposome dispersion may be dehydrated to form a lipid powder. The lipid powder may be further refined by any appropriate grinding or reducing process. The resultant lipid powder is particularly stable and may be stored for extended periods making it feasible to produce bulk quantities which may be stored until needed. In a preferred embodiment, the liposomes are combined with a bulking agent prior to dehydration and formation of the lipid powder.

The liposomes formed from either a film, or spray dried powder, after hydration with suitable hydrating solution such as sucrose, may be lyophilized. The lyophilized cake can be stored preferably in a sterile lyophilization vial and later rehydrated with sterile water for injection.

Alternatively, the drug lipid complex yielding stable liposomes may be extended to one or more suitable biologically active agents, including pharmaceutical agents, an oxygen carrier, a nutrient, a coagulant, a nucleic acid molecule, a nucleic acid vector, an antisense nucleic acid, a ribozyme, a contrast agent, diagnostic agent or a pheromone.

The pharmaceutical agent may be one or more chemotherapeutic agents, antibiotics, anti-viral agents, antifungal agents, antifungal antibiotics, anaesthetics, anti-inflammatory agents, enzymes, hormones, growth factor, a cytokine, a neurotransmitter, an immunogen or hemoglobin. Non limiting examples are itraconazole, clotrimazole, ravuconazole, econazole, posaconazole, enilaconazole, oxiconazole, sulconazole, miconazole, fluconazole, itraconazole, amikacin, doxorubicin, epirubicin, ampicillin, kanamycin, amphotericin B, nystatin, all-trans-retinoic acid, muramyl dipeptide, 1-beta-D-arabinofuranozidecytosine, ciprofloxacin, clodronate, cis-diaminodichloro platinum, cyclosporine, chloroquine, Cu/Zn superoxide dismutase, daunorubicin, ganciclovir, interleukin-2, leukotriene A4, mitoxantron, pentostam, cisplatin, prostaglandin E1, ribavirin, streptosotocin, suramin, muramyl tripeptide, ether lipids, vincristin, vinblastin, , ropivacaine, prilocaine, mepivacaine, tetracaine or etidocaine, morphine, fentanyl, alfentanil or sufentanil and like.

30

It will also be appreciated that the pharmaceutical compositions of the invention may also be developed dosage forms suitable to administer topically to the skin or mucosa, that is,

dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions.

- 5 Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject(TM), Bioject(TM), etc.) injection.

The formulations of the invention can also be administered intranasally or by inhalation,
10 typically as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.

- 15 The pressurised container, pump, spray, atomizer, or nebuliser contains a solution of the formulations of the invention comprising, for example, ethanol (optionally, aqueous ethanol) or a suitable alternative agent for dispersing, solubilising, or extending release of the active, the propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

20

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

25

In the case of aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1µg to 10 mg of voriconazole or pharmaceutically acceptable salts, solvates, or derivatives thereof. The overall daily dose will typically be in
30 the range 1 µg to 200 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The abovementioned pharmaceutical preparations can be manufactured in the usual manner according to known methods, for example by mixing the liposome composition with suitable excipients or carriers.

- 5 Fungal infections which may be treated by voriconazole have been extensively described in the literature, and include topical infections caused by, inter alia, *Candida* spp, *Trichophyton* spp, *Microsporum* spp or *Epidermophyton floccosum*; mucosal infections caused by *Candida* spp; systemic infections caused by, inter alia, *Candida* spp, *Cryptococcus neoformans*, *Aspergillus* spp, *Fusarium* spp, *Scedosporium* spp, *Coccidioides immitis*, *Paracoccidioides*
10 *brasiliensis*, *Histoplasma* spp or *Blastomyces dermatitidis*. Particular infections include, but are not limited to, fungal peritonitis, vaginal candidiasis and allergic rhinosinusitis. It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.
- 15 Thus, the present invention also provides a method of preventing or treating the topical or systemic infections comprising administering the pharmaceutical composition comprising voriconazole encapsulated lipid cores to the patients in need thereof.

- Further, the present invention also provides use of a pharmaceutical composition comprising
20 voriconazole encapsulated lipid cores in the manufacture of a medicament for treating topical or systemic fungal infection in patients in need thereof.

- It will be appreciated that the precise therapeutic dose of voriconazole will depend on the age and condition of the patient and the nature of the condition to be treated and will be at the
25 ultimate discretion of the attendant physician.

The following examples are for the purpose of illustration of the invention only and is not intended in any way to limit the scope of the present invention.

30 Examples

Example 1: Voriconazole Liposomal Eye drops

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	0.30
2	Soya-lecithin (Lipoid S-100)	6.51
3	α -tocopherol	0.02
4	Cholesterol	1.66
5	Chloroform	q.s. to 50 ml
Aqueous Phase		
6	Dextrose	5.00
7	Benzalkonium Chloride	0.1
8	Purified Water	q. s. to 100 ml

Process:

- (1) Voriconazole, soya-lecithin S-100, cholesterol and α -tocopherol were dissolved in chloroform to form the oil phase.
- 5 (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Dextrose and Benzalkonium chloride was dissolved in purified water to form the aqueous phase.
- (4) The lipid film then rehydrated with the aqueous phase of step (3).
- (5) Size of the vesicles was reduced by using high pressure homogenization or extrusion
- 10 followed by aseptic filtration of the liposomal solution.
- (6) Finally liposome solution filled in container, it then stoppered and sealed.

Example 2: Voriconazole Liposomal Eye drops

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	0.30
2	Soya-lecithin (Lipoid S-100)	6.51
3	α -tocopherol	0.02
4	Cholesterol	1.66

5	Chloroform	q.s to 50 ml
Aqueous Phase		
6	Sodium dihydrogen phosphate monohydrate	0.46
7	Anhydrous disodium hydrogen phosphate	0.47
8	Sodium chloride	0.41
9	0.8M HCl	q.s. to pH 6.8
10	Stabilized Oxychloro Complex	0.005
11	Purified Water	q. s. to 100 ml

Process:

- (1) Voriconazole, soya-lecithin S-100, cholesterol and α -tocopherol were dissolved in chloroform.
- 5 (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Sodium dihydrogen phosphate monohydrate, Anhydrous disodium hydrogen phosphate, Sodium chloride and Stabilized Oxychloro Complex were dissolved in purified water to form the aqueous phase.
- (4) The pH was adjusted to 6.8 with 0.8M HCl
- 10 (5) The lipid film then rehydrated with the aqueous phase formed in step (3).
- (6) Size of the vesicles was reduced by using high pressure homogenization or extrusion followed by aseptic filtration of the liposomal solution.
- (7) Finally liposome solution filled in container, it then stoppered and sealed.

15 Example 3: Voriconazole Liposomal Eye drops

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	0.30
2	Soya-lecithin (Lipoid S-100)	6.51
3	α -tocopherol	0.02
4	Cholesterol	1.66

5	Chloroform	q.s to 50 ml
Aqueous Phase		
6	Tris buffer (10mM)	0.121
7	Sodium chloride (140mM)	0.812
9	1 M HCl	q.s. to pH 6.8
10	Phenylmercuric nitrate	0.002%
11	Purified Water	q. s. to 100 ml

Process:

- 5 (1) Voriconazole, soya-lecithin S-100, cholesterol and α -tocopherol were dissolved in chloroform.
- (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Tris buffer, Sodium chloride, Phenylmercuric nitrate and 1 M HCl were dissolved in purified water to form the aqueous phase.
- 10 (4) The pH was adjusted to 6.8 with 1 M HCl
- (5) The lipid film then rehydrated with the aqueous phase formed in step (3).
- (6) Size of the vesicles was reduced by using high pressure homogenization or extrusion followed by aseptic filtration of the liposomal solution.
- (7) Finally liposome solution filled in container, it then stoppered and sealed.

15

Example 4: Voriconazole Liposomal Eye drops

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	0.30
2	Soya-lecithin (Lipoid S-100)	6.51
3	α -tocopherol	0.02
4	Cholesterol	1.66
5	Steryl amine	0.326
5	Chloroform	q.s to 50 ml

Aqueous Phase		
6	Tris buffer (10mM)	0.121
7	Sodium chloride (140mM)	0.812
9	1 M HCl	q.s. to pH 6.8
10	Benzalkonium Chloride	0.1
11	Purified Water	q. s. to 100 ml

Process:

- 5 (1) Voriconazole, soya-lecithin S-100, cholesterol, Steryl amine and α -tocopherol were dissolved in chloroform.
- (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Tris buffer, Sodium chloride and Benzalkonium Chloride were dissolved in purified water to form the aqueous phase.
- 10 (4) The pH was adjusted to 6.8 with 1 M HCl.
- (5) The lipid film then rehydrated with the aqueous phase formed in step (3).
- (6) Size of the vesicles was reduced by using high pressure homogenization or extrusion followed by aseptic filtration of the liposomal solution.
- (7) Finally liposome solution filled in container, it then stoppered and sealed.

15

Example 5: Voriconazole Liposomal Injection

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	1
2	Soya-lecithin (Lipoid S-100)	6
3	α -tocopherol	0.02
4	Cholesterol	1
5	Chloroform	q.s. to 50 ml
Aqueous Phase		
6	Dextrose	5.00

7	Benzyl alcohol	1%
8	Purified Water	q. s. to 100 ml

Process:

- (1) Voriconazole, soya-lecithin S-100, cholesterol and α -tocopherol were dissolved in
5 chloroform to form the oil phase.
- (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Dextrose and Benzyl alcohol was dissolved in purified water to form the aqueous phase.
- (4) The lipid film then rehydrated with the aqueous phase of step (3).
- (5) Size of the vesicles was reduced by using high pressure homogenization or extrusion
10 followed by aseptic filtration of the liposomal solution.
- (6) Finally liposome solution filled in container, it then stoppered and sealed.

Example 6: Voriconazole Liposomal Injection

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	1
2	Soya-lecithin (Lipoid S-100)	6
3	α -tocopherol	0.02
4	Cholesterol	1
5	Chloroform	q.s to 50 ml
Aqueous Phase		
6	Sodium dihydrogen phosphate monohydrate	0.46
7	Anhydrous disodium hydrogen phosphate	0.47
8	Sodium chloride	0.41
9	0.8M HCl	q.s. to pH 6.8
10	Chlorobutanol	0.4%
11	Purified Water	q. s. to 100 ml

Process:

- (1) Voriconazole, soya-lecithin S-100, cholesterol and α -tocopherol were dissolved in chloroform.
- (2) The resulting oil phase was rota-evaporated to form a lipid film.
- 5 (3) Sodium dihydrogen phosphate monohydrate, Anhydrous disodium hydrogen phosphate, Sodium chloride and Chlorobutanol were dissolved in purified water to form the aqueous phase.
- (4) The pH was adjusted to 6.8 with 0.8M HCl.
- (5) The lipid film then rehydrated with the aqueous phase formed in step (3).
- 10 (6) Size of the vesicles was reduced by using high pressure homogenization or extrusion followed by aseptic filtration of the liposomal solution.
- (7) Finally liposome solution filled in container, it then stoppered and sealed.

Example 7: Voriconazole Liposomal Eye drops

15

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	1
2	Soya-lecithin (Lipoid S-100)	6
3	α -tocopherol	0.02
4	Cholesterol	1
5	Chloroform	q.s to 50 ml
Aqueous Phase		
6	Tris buffer (10mM)	0.121
7	Sodium chloride (140mM)	0.812
9	1 M HCl	q.s. to pH 6.8
10	Benzyl alcohol	1%
11	Purified Water	q. s. to 100 ml

Process:

- (1) Voriconazole, soya-lecithin S-100, cholesterol and α -tocopherol were dissolved in chloroform.
- (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Tris buffer, Sodium chloride and Benzyl alcohol were dissolved in purified water to form the aqueous phase.
- (4) The pH was adjusted to 6.8 with 1 M HCl.
- (5) The lipid film then rehydrated with the aqueous phase formed in step (3).
- (6) Size of the vesicles was reduced by using high pressure homogenization or extrusion followed by aseptic filtration of the liposomal solution.
- (7) Finally liposome solution filled in container, it then stoppered and sealed.

Example 8: Voriconazole Liposomal Injection

Sr No.	Ingredients	Qty / Unit % w/v
Organic Phase		
1	Voriconazole	1
2	Soya-lecithin (Lipoid S-100)	6
3	α -tocopherol	0.02
4	Cholesterol	1
5	Steryl amine	0.326
5	Chloroform	q.s to 50 ml
Aqueous Phase		
6	Tris buffer (10mM)	0.121
7	Sodium chloride (140mM)	0.812
9	1 M HCl	q.s. to pH 6.8
10	Chlorobutanol	0.4%
11	Purified Water	q. s. to 100 ml

Process:

- (1) Voriconazole, soya-lecithin S-100, cholesterol, Steryl amine and α -tocopherol were dissolved in chloroform.
- (2) The resulting oil phase was rota-evaporated to form a lipid film.
- (3) Tris buffer, Sodium chloride and Chlorobutanol were dissolved in purified water to form
- 5 the aqueous phase.
- (4) The pH was adjusted to 6.8 with 1 M HCl
- (5) The lipid film then rehydrated with the aqueous phase formed in step (3).
- (6) Size of the vesicles was reduced by using high pressure homogenization or extrusion followed by aseptic filtration of the liposomal solution.
- 10 (7) Finally liposome solution filled in container, it then stoppered and sealed.

Example 9: Voriconazole Ready-To-Use Syrup

Sr No.	Ingredients	Qty (1% w/v)
LIPOSOME PART		
Organic Phase		
1	Voriconazole	1%
2	Soya-lecithin (Lipoid S-100)	3%
3	Cholesterol	0.3%
5	Chloroform	q.s
Aqueous Phase		
6	Purified water	q. s.
SYRUP BASE		
7	Propylene glycol	20%
8	Sorbitol	40%
9	Xanthan gum	0.1%
10	Glycerol	5%
11	Pineapple flavour	0.01%
12	Sodium Saccharin	0.1%

13	Quinoline Yellow	0.001%
14	Sodium Benzoate	0.2%
15	Purified water	q. s.

Process:**(A) Liposome Part**

- (1) Voriconazole, soya-lecithin S-100, cholesterol, Steryl amine and α -tocopherol were
5 dissolved in chloroform.
(2) The resulting oil phase was rota-evaporated to form a lipid film.
(3) The lipid film then rehydrated with purified water
(4) Size of the vesicles was reduced by using high pressure homogenization or extrusion.

(B) Syrup Base

- 10 (5) Sodium benzoate was dissolved in purified water.
(6) Xanthan gum was dispersed in glycerol separately and was added to the bulk obtained in
step (5)
(7) The liposomal dispersion obtained in step (4) was added to the dispersion obtained in step
(6) under stirring.
15 (8) Propylene glycol and sorbitol was added to the liquid mass obtained in step (7) under
stirring
(9) Separate solution of quinoline yellow and sodium saccharin was prepared and added to
the bulk obtained in step (8) under stirring
(10) Pineapple flavour was added to the syrup and the volume was made up by the addition
20 of purified water under stirring.

It will be readily apparent to one skilled in the art that varying substitutions and
modifications may be made to the invention disclosed herein without departing from the
spirit of the invention. Thus, it should be understood that although the present invention has
25 been specifically disclosed by the preferred embodiments and optional features, modification
and variation of the concepts herein disclosed may be resorted to by those skilled in the art,
and such modifications and variations are considered to be falling within the scope of the
invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

5

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a polymer" includes a single polymer as well as two or more different polymers; reference to a "plasticizer" refers to a single plasticizer or to
10 combinations of two or more plasticizer, and the like.

15

20

25

30

CLAIMS:

1. A pharmaceutical composition comprising liposomes and optionally one pharmaceutically acceptable excipient, wherein the liposomes comprises voriconazole or its pharmaceutically acceptable salts, solvates, derivatives, hydrates, enantiomers, polymorphs, prodrugs or mixtures thereof.
2. A composition according to claim 1, wherein the liposomes are prepared from phospholipids/lipid component such as egg yolk lecithin (phosphatidylcholine), soybean lecithin, cholesterol, lysolecithin, sphingomyelin, phosphatidic acid, phosphatidylserine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, diphenylphosphatidylglycerol, cardiolipin, plasmalogen, Hydrogenated soy phosphatidyl choline, dicetyl phosphate, distearoylphosphatidylcholine, dipalmitoylphosphatidylcholine, dipalmitoylphosphatidyl glycerol, distearoylphosphatidyl glycerol, dilaurylphosphatidylglycerol, dipalmitoylphosphatidylethanolamine, dipalmitoylphosphatidylserine, eleostearoylphosphatidylcholine, eleostearoylphosphatidylethanolamine, eleostearoylphosphatidylserine, dipalmitoylphosphatidyl acid, dipalmitoylphosphatidyl ethanolamine, their salts and the corresponding distearoyl- and dimyristyl- counterparts, and/or mixtures thereof.
3. A composition according to claim 1, wherein the ratio of voriconazole to lipid/phospholipid is from 1:1 to 1:15.
4. A composition according to claims 1, 2 or 3 further comprising a lipid carrier.
5. A composition according to claim 1, 2,3 or 4, further comprising a pharmaceutically acceptable pH adjusting agent.
6. A composition according to any one of the preceding claims, further including an antioxidant.

7. A composition according to claim 6, wherein the antioxidant is α -tocopherol, (BHT) butylhydroxytoluene, (BHA) butylhydroxyanisole, propyl gallate, ascorbic acid, and water soluble iron and calcium chelator such as ethylenediaminetetraacetic acid biethylenediaminepentaacetic acid, and ED3A.

5

8. A composition according to any one of the preceding claims, further comprising a rehydrating solution.

9. A composition according to claim 8, wherein the rehydrating solution is water or
10 water comprising dissolved salt(s), saccharides or a buffer.

10. A composition according to any one of the preceding claims, further including a charge inducing agent.

15 11. A composition according to claim 10, wherein the charge inducing agent is stearylamine, cetyl pyridinium chloride, lipoaminoacid and dicetyl phosphate or a combinations thereof.

12. A composition comprising voriconazole and phospholipid / lipid, lipid carrier and
20 organic solvent.

13. A process for making liposomes comprising a lipid core comprising voriconazole, said process comprising dissolving the voriconazole, and one or more phospholipids/lipid components, in an organic solvent, and evaporating the organic solvent.

25

14. A process according to claim 13, wherein one or more lipid carriers, and/or one or more antioxidants are additionally dissolved in the lipid core.

15. A process according to claim 14, wherein the lipid carrier is hydrogenated egg
30 phosphatidylcholine, hydrogenated soya lecithin, hydrogenated soya phosphatidylcholine and distearoyl or dipalmitoyl phosphatidylcholine, surfactants, solvents:

We would like to remove this claim

16. A process according to claim 13, 14 or 15, wherein the evaporation step comprises comprising drying the lipid solution to form a drug-lipid film.

5 17. A process according to claim 16, further comprising rehydrating the drug-lipid film with a rehydrating solution to form a liposome solution.

18. A process according to claim 17, wherein the rehydrating solution is water or water containing dissolved salt(s), saccharides or a buffer.

10

19. A process according to claim 18, further comprising reducing the vesicle size of the liposomes of the liposome solution to a desired size.

20. A process according to claim 18 or 19, further comprising aseptic filtration of the
15 liposome solution.

21. A process according to claim 20, further comprising filling the liposome solution in a suitable container and sealing the container.

20 22. A pharmaceutical composition as claimed in claim 1 in the form of a ophthalmic dosage form.

23. A pharmaceutical composition as claimed in claim 1 in the form of a parenteral dosage form.

25

24. A pharmaceutical composition as claimed in claim 1 in the form of oral dosage forms.

25. A pharmaceutical composition as claimed in claim 24 wherein the oral dosage forms comprises tablet, capsule and liquids.

30

26. A pharmaceutical composition according to any one of claims 1 to 12 and claims 22 to 25 for use in the prevention or treatment of topical or systemic fungal infections. .

27. The use of a pharmaceutical composition according to any one of claims 1 to 12 and claims 22 to 25 in the manufacture of a medicament for use in the prevention or treatment of topical or systemic fungal infections.

5

28. A method of preventing or treating the topical or systemic fungal infections comprising administering a pharmaceutical composition according to any one of claims 1 to 12 and claims 22 to 25 to a patient in need thereof.

10 29. A method of improving the aqueous stability voriconazole comprising encapsulating voriconazole in the lipid cores of liposomes.