TOPICAL ANHYDROUS AND ETHANOL-FREE ASCOMYCIN COMPOSITIONS

The invention relates to topical pharmaceutical compositions comprising an ascomycin for the treatment of skin disorders, in the form of a single-phase liquid or semi-solid composition substantially free of ethanol and water.

Ascomycins such as ascomycin itself or derivatives thereof are examples of compounds of the FK 506 class. FK506 (tacrolimus) is a known macrolide antibiotic that is produced by Streptomyces tsukubaensis No. 9993. It is also a potent immunosuppressant. The structure of FK506 is given in The Merck Index 12th Edition (1996) on p. 546 as entry 9200. Methods of preparing FK506 are described in e.g. EP 184162.

A large number of derivatives, antagonists, agonists and analogues of FK506, which retain the basic structure and at least one of the biological properties (for example the immunological properties) of FK506, are now known. These compounds are described in a large number of publications, for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385 and WO 93/5059. Ascomycin and derivatives thereof, including FK506, are referred to hereinafter as "ascomycins".

Ascomycins are known to be indicated for use in e.g. the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses. The condition of the skin to be treated may vary e.g. with kind and grade of disease; e.g. the skin may be dry or fatty skin. Furthermore, the skin to be treated may be haired. There is a need for a pharmaceutical composition that may be applied to the skin substantially independently of the condition of the skin.

It has now been found that an ascomycin can be formulated into a pharmaceutical composition in the form of a single-phase liquid or semi-solid topical formulation substantially free of ethanol and water. These pharmaceutical compositions are effective independently of the condition of the skin, nail or mucosa, are well tolerated, stable and have particularly interesting penetration properties.

They surprisingly retain and improve on the beneficial penetration properties of more complex or inhomogenous formulations such as water- or hydrocarbon-based emulsions or suspensions, while being particularly convenient in terms of ease of administration and patient compliance.

Thus it has been found that a large part of the bulk of the compositions, at least 40 % w/w, can consist of simple solvents, resulting in easily-applicable, clear liquid solutions or thickened, semi-solid solutions.

In particular, the invention concerns a **single-phase topical liquid or semi-solid pharmaceutical composition** substantially **free of ethanol and water** which comprises **an ascomycin** in a carrier vehicle comprising **a 3-component solvent mixture** amounting to **at least 40 % w/w of the total weight** of the composition and consisting of:

i) a **C_{3-8} alkanol** and/or **C_{1-8} alkanediol;**

ii) a **fatty alcohol**; and

iii) a **further solvent** selected from:

a) an **alkane carboxylic acid alkyl ester** and/or **alkane dicarboxylic acid alkyl ester** and/or

b) a **hydrophilic co-component** and/or

c) a **triglyceride;**

and optionally further conventional excipients;

hereinafter briefly named **"the compositions of the invention".**

The compositions of the invention have the advantage that they consist of few components, are straightforward to prepare and are well-tolerated on human skin.

The compositions of the invention may be e.g. in the form of a topical solution or a spray solution, a gel, a foam or an ointment, preferably they are in the form of a gel, a foam or an ointment.

Semi-solid or foamy compositions are preferred.

"Single-phase" means herein that the compositions of the invention are other than multiphasic, e.g. other than two-phase systems such as creams or emulsions; they may be in any single-phase form, e.g. as a solution or spray solution, a gel, an ointment or e.g. the liquid component of a foam, whereby the active ingredient normally is in dissolved form.

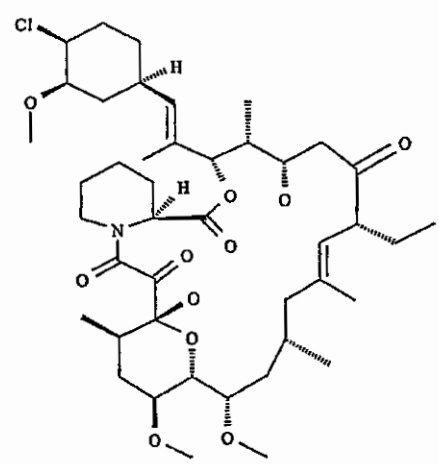
"Liquid or semi-liquid" means that the compositions of the invention are essentially solutions in liquid or solidified liquid form.

"Substantially free of ethanol and water" means that neither ethanol nor water is added as an intentional constituent part of the compositions of the invention. However, e.g. a small amount of humidity, e.g. up to about 1 % water w/w, may nevertheless be present, e.g. as an intrinsic impurity in some of the excipients used, or as part of the active ingredient when this is e.g. a hydrate, e.g. when crystal form A (see WO 99/01458) of compound A hereinafter is used.

A particularly beneficial aspect of the compositions of the invention is that while the components of the above 3-component solvent mixture are solubilizing agents, they additionally may possess penetration enhancing properties, thus contributing to keeping the formulations both simple and effective. Further, it has been found that the solutions may be thickened without any apparent loss in efficacy.

Preferred ascomycins include e.g.:

- FK506 (**tacrolimus**);
- 32-[4-(3,5-dimethoxyphenyl)imidazol-1-ylmethoxy]ascomycin (**L-733725**) (in Example 1 and as compound of formula I in WO 97/8182);
- 32-O-(1-hydroxyethylindol-5-yl)ascomycin (**L-732531**) (Transplantation 65 [1998] 10-18, 18-26, Figure 1 on page 11);
- (32-desoxy-32-epi-N1-tetrazolyl)ascomycin (**ABT-281**) (J. Invest. Dermatol. 12 [1999] 729-738, Figure 1 on page 730);
- 33-epichloro-33-desoxy-ascomycin (**pimecrolimus**), i.e. {[1E-(1R,3R,4S)]1R,9S,12S,13R, 14S,17R,18E, 21S,23S,24R,25S,27R}-12-[2-(4-chloro-3-methoxycyclohexyl)-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28,dioxa-4-azatricyclo [22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetraone, of formula I



disclosed as Example 66a in e.g. EP 427680 (hereinafter referred to as **Compound A**);

- {[1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16, 20-trihydroxy-4-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-azatricyclo[18.6.1.0(1,22)]heptacos-10-ene-2,8,21,27-tetraone disclosed as Examples 6d and 71 in e.g. EP 569337 (hereinafter referred to as **Compound B**); and
- {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0(4,9)]octacosa-5,18-diene-2,3,10,16-tetraone, also known as 5,6-dehydro-ascomycin, disclosed as Example 8 in e.g. EP 626385 (hereinafter referred to as **Compound C**).

While the 3-component solvent mixture, as indicated above, amounts to at least 40 % w/w of the total weight of the composition, which may thus optionally contain further conventional ingredients, it preferably amounts to more than 40 %, e.g. from about 55 % to almost about 100 %, preferably from about 80 % or about 90 % to about 99.95 %, even more preferably from about 95 % to about 99.50 % of the total weight.

Components i) and ii) each independently preferably amount to up to about 50 %, more preferably up to about 20 %, especially up to about 15 % of the total weight. In sum, they preferably amount to up to about 60 %, preferably up to about 40 %, especially up to about 30 % of the total weight.

Component iii) preferably amounts to up to about 75 %, more preferably up to about 65 % of the total weight of the composition, it is preferably from about 30 % to about 75 % of the total weight.

The active agent is e.g. present in the compositions of the invention in an amount of from about 0.05 % to about 10 % by weight, e.g. from 0.1 % to 6 % by weight, preferably from 1 % to 5 % by weight based on the total weight of the composition.

C_{3-8} alkanol component i) preferably is a straight or branched chain saturated alkanol, e.g. isopropanol. **C_{1-8} alkanediol component i)** preferably is propylene glycol (i.e. 1,2-propanediol), butylene glycol, 2-ethyl-1,3-hexanediol and hexylene glycol (i.e. 2-methyl-2,4-pentanediol), especially propylene glycol and hexylene glycol.

Preferably the ascomycin and component i) in the compositions are present, at least initially, in a weight ratio of about 0.05 to 10 : 10 to 60, more preferably in a weight ratio of about 0.5 to 10 : 50 to 60, even more preferably in a weight ratio of about 1 to 3 : 50 to 60. However, upon administration to skin the more volatile components, e.g. lower alkanols, may evaporate to yield a supersaturated solution which may contribute to further enhance penetration.

Component ii) preferably is a mono- or polyunsaturated fatty alcohol, for example a C_{12-24}, e.g. C_{16-18} mono- or polyunsaturated fatty alcohol, preferably oleyl alcohol or elaidic alcohol; especially preferred is oleyl alcohol.

Preferably the ascomycin and component ii) in the compositions are present in a weight ratio of about 0.05 to 10 : 5 to 90, more preferably in a weight ratio of about 0.5 to 10 : 5 to 50, even more preferably in a weight ratio of about 1 to 5 : 10 to 20.

Component iii)a) preferably is a C_{12-24}, preferably C_{14-16} carboxylic acid alkyl ester, e.g. isopropyl myristate, ethyl myristate or isopropyl palmitate, especially isopropyl myristate or palmitate, or a C_{2-10} alkane dicarboxylic acid alkyl ester, e.g. diisopropyl adipate or diethyl adipate, especially diisopropyl adipate.

Component iii)b) preferably is a pharmaceutically acceptable ether diol, e.g. dipropylene glycol or diethylene glycol; a diether alcohol, e.g. diethyleneglycol mono ethyl ether; a di- or partial ether of a low molecular weight mono- or polyoxyalkanediol, e.g. tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol^{R}); diethylene glycol monoethyl ether (Transcutol^{R}); triethyl citrate; N-methylpyrrolidone; dimethylisosorbide (i.e. 1,4:3,6-dianhydro-2,5-di-O-methyl-D-glucitol); or propylene carbonate; especially dimethylisosorbide.

Component iii)c) preferably consists of medium-chained triglycerides, such as Miglyol 812^{R}.

The compositions of the invention may optionally comprise **further conventional excipients**, e.g., for easier application, a thickened solution may be desirable, e.g. a semi-solid solution or a fluid-gel or a transparent gel. This can be achieved by adding conventional **consistency agents** (viscosity-enhancing agents) to enhance the viscosity of the compositions.

Suitable **consistency agents** include e.g.:

- polyacrylic acid, as known under the names carboxypolymethylen, or carboxyvinylpolymer, or carbomer, or Carbopol^{R},
- cellulose derivatives, including e.g. ethyl-, propyl-, methyl-, hydroxypropyl- and hydroxypropylmethyl-celluloses,
- colloidal silicon dioxide, e.g. Aerosil^{R}, e.g. Aerosil R972^{R} or Aerosil 200^{R},
- polyvinyl alcohol,
- bee wax,
- hydrogenated castor oil (Cutina HR^{R}),
- polyvinyl pyrrolidone,
- polymethylacrylate resins, e.g. Eudispert^{R} or Eudragit^{R}, and
- solid alcohols, having e.g. a C_{12-24} chain, e.g. cetyl alcohol and/or stearyl alcohol, commercially available e.g. under the trademarks Lorol^{R} C16 and Lorol^{R} C18, respectively, from Henkel, Germany;

preferably hydroxypropylcellulose, colloidal silicon dioxide, bee wax, hydrogenated castor oil, polyvinylpyrrolidone or Eudragit^{R}.

Further conventional excipients are e.g. an **ointment base**, such as mineral hydrocarbons, e.g. liquid paraffin, petrolatum and microcrystalline wax. The ointment base, where its presence is appropriate, is in an amount of e.g. from about 0.1 % to about 40 %, e.g. from about 30 % to about 40 % of the total weight of the composition.

The compositions may also include **anti-oxidants** such as butyl-hydroxytoluene, ascorbyl palmitate, sodium pyrosulfite, butyl hydroxyanisole, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate and tocopherol, as appropriate. Furthermore, the addition of **preservatives** such as benzyl alcohol, parabens, sorbic acid and phenyl alcohol serves to prevent bacterial growth. Where the presence of anti-oxidants and/or preservatives is appropriate, they are preferably present in an amount of from about 0.01 % to about 2.5 % w/w each.

The compositions of the invention preferably are **devoid of surfactant**, except as required during processing to e.g. a foam formulation, and are substantially free of ethanol and water, as defined above.

For the treatment of fatty or hairy skin, non-greasy formulations are preferred, such as provided in e.g. Examples 1 to 17, 22 and 23 hereunder. Absence of greasiness and low residue upon application may lead to increased convenience especially on haired skin.

The components of the compositions of the invention are described in i.a. H.P. Fiedler, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), the contents of which are hereby incorporated by reference.

Particularly preferred are compositions of the invention wherein the ascomycin is e.g. pimecrolimus and

- component i) is isopropanol and/or hexylene glycol;
- component ii) is oleyl alcohol; and
- component iii) is:
  a) diisopropyl adipate and/or isopropyl myristate and/or
  b) dimethyl isosorbide and/or
  c) medium-chain triglycerides;

and optionally further conventional excipients;
especially the compositions of Examples 17 to 20 and 23, particularly Example 17 hereunder.

The compositions of the invention are indicated for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases. The terms "skin" and "cutaneous" should be understood broadly as comprising also diseases of e.g. nail or mucosa. Examples of immunologically-mediated diseases include alopecia areata, psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, and lupus erythematous. Examples of skin diseases include dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, acne, autoimmune diseases such as chronic rheumatoid arthritis, scleoderma and the like.

The invention further provides a **composition** as defined above **for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.**

It further provides a **method for treating inflammatory and hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases** comprising administering a composition of the invention to the skin of a patient in need thereof.

Still further, it provides the **use** of a composition of the invention **in the preparation of a medicament** for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

It further provides the **use of a carrier vehicle** as defined above **to enhance penetration** of an ascomycin into human skin, nail or mucosa.

The compositions of the invention may be prepared in conventional manner by working up the components into a pharmaceutical composition. For example, the compositions of the invention may be obtained by dissolving an ascomycin in a pharmaceutically acceptable alkanol, e.g. a C_{3-8} alkanol, a C_{1-8} alkanediol and/or a fatty alcohol. Other components, e.g. alkane carboxylic alkyl esters and/or alkane dicarboxylic esters, and/or hydrophilic co-components, triglycerides and optional further conventional excipients, may be added at the appropriate time as is conventional.

The following **Examples** illustrate the invention. They are not limitative.

All percentages referred to herein are weight/weight (% w/w) except where otherwise indicated. The term "stable" should be understood to mean that no separation of components of the respective composition is observed when stored at room temperature for a period of at least 3 months or longer and that there is no decomposition of active agent. However, some unintentional crystallization may occasionally take place e.g. upon storage, and the presence of a small amount of active ingredient in crystallized form in the compositions of the invention should thus be understood to still fall within the ambit of the invention.

Chemical analysis of the active agent is undertaken using reverse phase HPLC with UV detection; $\lambda = 210$ nm. Quantification limit is 0.1 % by weight.

In Examples 1 to 25, Compound A (pimecrolimus) may be replaced with Compound B; Compound C; tacrolimus; L-733725; L-732531; and ABT-281.

Examples 1 and 2 (solutions) and 3 (single-phase gel)

The following compositions are prepared:

Ingredients	Ex. 1	Ex. 2	Ex. 3
Compound A	1.0	8.0	1.0
i) isopropanol	49.0	42.0	47.0
propylene glycol	-	-	-
ii) oleyl alcohol	10.0	10.0	10.0
iii) a) isopropyl myristate	40.0	-	40.0
iii) b) dimethylisosorbide	-	40.0	-
Further ingredients:			
hydroxypropyl cellulose (consistency agent)	-	-	2.0

The compositions of Examples 1 to 3 are stable.

Examples 4 to 9 (solutions)

The following compositions are prepared:

Ingredients	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9
Compound A	1.0	1.0	1.0	1.0	1.0	1.0
i) isopropanol	39.0	39.0	39.0	39.0	39.0	39.0
hexylene glycol	-	-	10.0	10.0	10.0	10.0
ii) oleyl alcohol	10.0	10.0	10.0	10.0	10.0	10.0
iii) a) isopropyl myristate	-	-	40.0	-	-	-
isopropyl palmitate	-	-	-	40.0	-	-
diisopropyl adipate	-	50.0	-	-	-	40.0
iii) b) dimethyl isosorbide	50.0	-	-	-	40.0	-

The compositions of Examples 4 to 9 are stable.

Examples 10 to 15 (solutions)

The following compositions are prepared:

Ingredients		Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 15
Compound A		2.0	2.0	0.5	0.5	5.0	2.0
i)	propylene glycol	38.0	38.0	-	-	-	-
	hexylene glycol	-	-	39.5	39.5	35.0	38.0
ii)	oleyl alcohol	10.0	10.0	10.0	10.0	10.0	10.0
iii) a)	isopropyl myristate	-	-	50.0	-	-	-
	isopropyl palmitate	-	-	-	50.0	-	-
	diisopropyl adipate	-	50.0	-	-	-	50.0
iii) b)	dimethyl isosorbide	50.0	-	-	-	50.0	-

The compositions of Examples 10 to 15 are stable.

Examples 16 and 17 (solutions)

The following compositions are prepared:

Ingredients		Ex. 16	Ex. 17
Compound A		1.0	1.0
i)	isopropanol	-	10.0
	hexylene glycol	5.0	5.0
ii)	oleyl alcohol	10.0	10.0
iii) a)	diisopropyl adipate	84.0	74.0

The compositions of Examples 16 and 17 are stable.

Examples 18 to 21 (semi-solid ointments)

The following compositions are prepared:

Ingredients	Ex. 18	Ex. 19	Ex. 20	Ex. 21*
Compound A	1.0	1.0	1.0	0.3
i) isopropanol	10.0	10.0	10.0	-
hexylene glycol	5.0	5.0	5.0	10.0
ii) oleyl alcohol	10.0	10.0	10.0	10.0
iii) a) diisopropyl adipate	32.0	54.0	64.0	-
iii) c) medium-chain triglycerides (Miglyol 812)	-	-	-	44.0
Further ingredients:				
liquid paraffin (ointment base)	32.0	-	-	29.7
colloidal silicon dioxide (Aerosil R972) (consistency agent)	10.0	-	-	6.0
bee wax (consistency agent)	-	20.0	-	-
hydrogenated castor oil (Cutina HR) (consistency agent)	-	-	10.0	-

* oleogel

The compositions of Examples 18 to 21 are stable.

Examples 22 to 25 (solutions)

The following compositions are prepared:

Ingredients	Ex. 22	Ex. 23	Ex. 24	Ex. 25
Compound A	0.8	4.0	0.6	0.2
i) isopropanol	10.0	10.0	10.0	-
hexylene glycol	5.0	5.0	10.0	10.0
ii) oleyl alcohol	10.0	10.0	10.0	10.0
iii) a) isopropyl myristate	-	-	-	49.8
diisopropyl adipate	-	71.0	-	-
iii) c) medium-chain triglycerides (Miglyol 812)	74.2	-	39.4	-
Further ingredients:				
liquid paraffin (ointment base)	-	-	30.0	30.0

The compositions of Examples 22 to 25 are stable.

The utility of the compositions of the invention can be observed in standard clinical tests such as the test set out below using a concentration of 0.005 % to 10 % w/w (preferably 0.1 % to 3 % w/w) of the active agent.

A representative clinical trial is carried out as follows:

A randomised double-blind, vehicle-controlled within-patient study comparing the composition of the invention at a dose of 0.1 % to 3 % by weight (based on the total weight of the composition) active agent on the diseased skin area, e.g. 200 cm^2, corresponding to about 0.5 to 50 mg/cm^2, preferably 1 to 10 mg/cm^2 of composition, and placebo on the diseased skin area as positive control is performed in patients suffering from inflammatory and hyperproliferative skin diseases or of cutaneous manifestations of immunologically-mediated diseases.

The patients are treated with the composition twice daily for six months. The therapeutic effect is evaluated and the time to partial clearance is used for efficacy. Local tolerability of study medications and routine safety parameters, including haematology and clinical chemistry, are recorded.

The utility can also be observed using the established assay of experimentally induced allergic contact dermatitis in young domestic pigs (J. Investig. Dermatol. 98 [1992] 851-855). Several formulations were tested for inhibition of inflammatory changes (intensity and extent of redness and infiltration) by clinical examination. Efficacy was evaluated by comparison of inflammatory changes in treated and untreated contralateral test sites in the same animals. Results obtained are as follows:

Formulation of Example No.	Efficacy vs. untreated sites (mean %; n = 12**)
16	79
17	73
18	78
20	70
Pimecrolimus cream 1 %	68

** each formulation was tested in 2 test sites in 6 animals

The exact amount of composition of the invention to be administered depends on various factors, for example the desired duration of treatment and the rate of release of the active agent. Satisfactory results are obtained in larger mammals, for example humans, with the local application over the area to be treated of a 0.05 % to 10 % w/w, preferably 0.1 % to 3 %, concentration of the active agent once or several times a day (for example 2 to 5 times a day). In general the composition may be applied to areas of skin as small as 1 cm^2 to as large as 0.5 m^2, preferably the composition will be applied to the head area in the treatment of inflammatory and hyperproliferative skin diseases or of cutaneous manifestations of immunologically-mediated diseases. Suitable skin loadings of the active agent fall within the range of 0.005 mg/cm^2 to 1 mg/cm^2.

The compositions of the invention are found to be effective independently of the condition of the skin and are well tolerated on skin. They may be easily applied to large areas of skin using a conventional applicator, e.g. brush, cotton pad, filament, topical spray or roller ball applicator, and are thus very convenient in use.

Claims:

1. A a single-phase topical liquid or semi-solid pharmaceutical composition substantially free of ethanol and water which comprises an ascomycin in a carrier vehicle comprising a 3-component solvent mixture amounting to at least 40 % w/w of the total weight of the composition and consisting of:
   i) a C_{3-8} alkanol and/or C_{1-8} alkanediol;
   ii) a fatty alcohol; and
   iii) a further solvent selected from:
      a) an alkane carboxylic acid alkyl ester and/or alkane dicarboxylic acid alkyl ester and/or
      b) a hydrophilic co-component and/or
      c) a triglyceride;

   and optionally further conventional excipients.

2. A composition according to claim 1 wherein the ascomycin is pimecrolimus.

3. A composition according to claim 1 or 2 wherein
   - component i) is isopropanol and/or hexylene glycol;
   - component ii) is oleyl alcohol; and
   - component iii) is:
     a) diisopropyl adipate and/or isopropyl myristate and/or
     b) dimethyl isosorbide and/or
     c) medium-chain triglycerides;

   and optionally further conventional excipients.

4. A composition according to claim 1 or 2 comprising further conventional excipients selected from hydroxypropyl cellulose, liquid paraffin, colloidal silicon dioxide, bee wax and hydrogenated castor oil.

5. A composition according to claim 1 or 2 wherein the ascomycin is present in an amount of 1 % to 5 % by weight of the composition.

6. A composition according to claim 1 or 2 which is in the form of a gel, a foam or an ointment.

7. A composition according to claim 1 or 2 for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

8. Use of a composition according to claim 1 or 2 in the preparation of a medicament for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

9. Use of a carrier vehicle as defined in claim 1 to enhance penetration of an ascomycin into human skin, nail or mucosa.