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(54) Title: COMPOSITIONS COMPRISING MACROLIDE T-CELL IMMUNOMODULATORS OR IMMUNOSUPPRES-
SANTS IN COMBINATION WITH ANTIBACTERIALS

(57) Abstract: Highly compatible or synergistic combinations of a macrolide T-cell immunomodulator or immunosuppressant such as 33-epichloro-33-desoxyascomycin and an antibacterial such as sulfasalazin, ciprofloxacin, ofloxacin, erythromycin or gentamycin, optionally with a further pharmaceutically active agent, especially a retinoid, are provided, which are useful in particular in the treatment of diseases involving bacterial or suspected or anticipated bacterial infection, for immunomodulation or immunosuppression in conditions in which bacterial or suspected or anticipated bacterial colonisation of e.g. the skin plays a role, such as atopic, contact and seborrhoeic dermatitis, eczema, psoriasis, acne, rosacea, post-peel, skin burning, itching, or IBD, and in situations of bacterial resistance.



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COMPOSITIONS COMPRISING MACROLIDE T-CELL IMMUNOMODULATORS OR IMMUNOSUPPRESSANTS
IN COMBINATION WITH ANTIBACTERIALS

The invention relates to pharmaceutical compositions, for use in particular in the treatment of skin diseases. It concerns a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial.

It has now been found that, surprisingly, macrolide T-cell immunomodulators and immunosuppressants, when used in combination with antibacterials, are highly compatible or may even act synergistically, such that effective beneficial, especially antibacterial activity is seen upon co-administration at dosages which may be kept high but are free of negative interaction.

The invention thus concerns novel pharmaceutical compositions comprising a **macrolide T-cell immunomodulator or immunosuppressant** in association or combination with an **antibacterial**, hereinafter briefly named "the compositions of the invention".

A macrolide T-cell immunomodulator or immunosuppressant is to be understood herein as being a T-cell immunomodulator or T-cell immunosuppressant which has a macrocyclic compound structure including a lactone or lactam moiety. While it preferably has at least some T-cell immunomodulating or immunosuppressant activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as anti-inflammatory activity.

An antibacterial is to be understood herein as being an agent directed against a pathogenic bacterium, namely a prokaryotic microbe which is capable of causing disease in animals, especially humans.

The compositions of the invention may be adapted for systemic, e.g. oral or intravenous, or for topical use; preferably they are adapted for topical use. They are useful for the known indications of the particular active agents incorporated therein. They are particularly indicated for use in diseases involving bacteria, optionally in connection with an inflammatory component or inflammatory complications, such as atopic, contact and seborrhoeic dermatitis, eczema, psoriasis, acne, rosacea, post-peel, skin burning, itching or inflammatory bowel disease (IBD), or in situations of bacterial resistance.

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A suitable **macrolide T-cell immunomodulator or immunosuppressant** is for example an FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor, in particular an **asco-** or **rapamycin**. It preferably is an ascomycin, especially an anti-inflammatory ascomycin derivative. While the macrolide preferably has at least some calcineurin- or mitogen-activated kinase modulating or inhibiting activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as antiinflammatory activity. It preferably is a compound, e.g. an ascomycin, having rather long-acting activity relatively to other members of the same structural class, e.g. it is metabolically degraded slowly to inactive products.

An asco- or rapamycin is to be understood as asco- or rapamycin as such, or a derivative thereof. An asco- or rapamycin derivative is to be understood as being an antagonist, agonist or analogue of the parent compound which retains the basic structure and modulates at least one of the biological, for example immunological properties of the parent compound.

An "anti-inflammatory ascomycin derivative" is defined herein as an ascomycin derivative that exhibits pronounced anti-inflammatory activity in e.g. animal models of allergic contact dermatitis but has only low potency in suppressing systemic immune response, namely, which has a minimum effective dose (MED) of up to a concentration of about 0.04 % w/v in the murine model of allergic contact dermatitis upon topical administration, while its potency is at least 10 times lower than for tacrolimus (MED 14 mg/kg) in the rat model of allogeneic kidney transplantation upon oral administration (Meingassner, J.G. et al., Br. J. Dermatol. 137 [1997] 568-579; Stuetz, A. Seminars in Cutaneous Medicine and Surgery 20 [2001] 233-241). Such compounds are preferably lipophilic.

Suitable **ascomycins** are e.g. as described in EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 523088, EP 532089, EP 569337, EP 626385, WO 93/5059 and WO 97/8182; in particular:

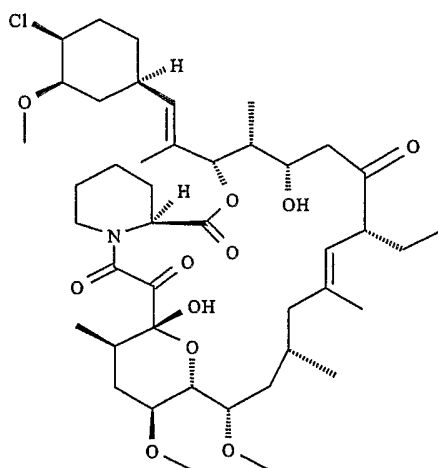
- **ascomycin**;
- **tacrolimus** (FK506; Prograf^R);
- **imidazolylmethoxyascomycin** (WO 97/8182 in Example 1 and as compound of formula I);

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- **32-O-(1-hydroxyethylindol-5-yl)ascomycin** (L-732531) (*Transplantation* **65** [1998] 10-18, 18-26, on page 11, Figure 1; and
- **(32-desoxy-32-epi-N1-tetrazolyl)ascomycin** (ABT-281) (*J.Invest.Dermatol.* **12** [1999] 729-738, on page 730, Figure 1);

preferably:

- {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)]octacos-5,18-diene-2,3,10,16-tetraone (Example 8 in EP 626385), hereinafter referred to as "**5,6-dehydroascomycin**";
- {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 (Examples 6d and 71 in EP 569337), hereinafter referred to as "**ASD 732**"; and especially
- **pimecrolimus** (INN recommended) (ASM981; ElidelTM), 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



(Example 66a in EP 427680), hereinafter also referred to as "**33-epichloro-33-desoxyascomycin**".

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Suitable anti-inflammatory ascomycin derivatives are e.g.: (32-desoxy-32-epi-N1-tetrazolyl)ascomycin (ABT-281); 5,6-dehydroascomycin; ASD 732; and pimecrolimus.

Suitable **rapamycins** are e.g. as described in USP 3'929'992, WO 94/9010 and USP 5'258'389, preferably **sirolimus** (rapamycin; Rapamune^R) and **everolimus** (RAD001; Certican^R).

A particularly preferred macrolide T-cell immunomodulator or immunosuppressant is **pimecrolimus**; it is in free form unless specified otherwise.

A suitable **antibacterial** is for example:

- salicylic acid or a salicylic acid derivative, such as: 4-aminosalicylic acid (Apacil^R) or 5-aminosalicylic acid (mesalamine; mesalazin; Asacol^R) or derivatives thereof, e.g. olsalazin (dimer of mesalamine; 5,5'-azabis[salicylic acid]) or sulfasalazin (5-[p-(2-pyridylsulfamoyl)phenylazo]salicylic acid; Azulfidine^R);
- a sulfonamide such as sulfacetamide or sulfadiazin;
- an antibiotic such as:
 - a) a penicillin, e.g. penicillin as such or cloxacillin;
 - b) an amoxicillin; a tetracyclin, e.g. tetracyclin as such, doxycyclin, oxytetracyclin or minocyclin; or a cephalosporin, e.g. ceftazidime or a cephalosporin as described in WO 96/35692, WO 98/43981 and WO 99/48896;
 - c) a quinolone such as ciprofloxacin, ofloxacin, norfloxacin, levofloxacin or lomefloxacin;
 - d) a macrolide antibiotic such as erythromycin;
 - e) clindamycin;
 - f) chloramphenicol or azidamfenicol (Leukomycin N^R); or
 - g) an aminoglycoside such as gentamycin, kanamycin, neomycin or tobramycin;
 - h) a polyene such as natamycin;
 - i) a pseudomonic acid such as mupirocin (pseudomonic acid A);
 - j) cefuroxim;
 - k) omiganan (MBI-594; MBI-226) as described in WO 98/07745; or
 - l) a pleuromutilin;

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- fusidic acid (ramycin) and derivatives thereof;
- metronidazol; or
- a polypeptide glycopeptide such as batracin, polymyxin, e.g. polymyxin B, or tyrothricin; preferably a salicylic acid derivative, a penicillin, a quinolone, a macrolide antibiotic or an aminoglycoside; especially sulfasalazin, penicillin, ciprofloxacin, ofloxacin, erythromycin or gentamycin; especially sulfasalazin, ciprofloxacin, ofloxacin, erythromycin or gentamycin; even more preferably ciprofloxacin or erythromycin. It is e.g. active against gram-positive bacteria such as Streptococcus and Staphylococcus or gram-negative bacteria such as Pseudomonas, Escherichia, Enterobacter, Klebsiella, Moraxella and Enterococcus.

Subgroups of compositions of the invention comprise a macrolide T-cell immunomodulator or immunosuppressant, preferably an anti-inflammatory ascomycin derivative as defined above, especially pimecrolimus, in combination or association with an antibacterial other than the following antibacterials singly or collectively in any number:

- an antibiotic; and/or
- an antibiotic of group a) and/or group b) as defined above; and/or
- a quinolone antibiotic of group c) as defined above; and/or
- erythromycin; and/or
- chloramphenicol; and/or
- sulfasalazine; and/or
- ciprofloxacin; and/or
- ofloxacin; and/or
- metronidazol; and/or
- a tetracyclin antibiotic; and/or
- salicylic acid and/or a salicylic acid derivative; and/or
- gentamycin; and/or
- bacitracin.

Defective skin in lesions can enhance bacterial colonization, and bacterial infection can enhance inflammation. Preferred for use in the treatment of conditions where inflammation is involved are compositions of the invention wherein one or both components

possess some degree of inherent anti-inflammatory activity. Particularly preferred are compositions comprising an ascomycin in combination with an antibacterial, especially 33-epichloro-33-desoxyascomycin in combination with sulfasalazin, ciprofloxacin, ofloxacin, erythromycin or gentamycin. The inflammatory condition is e.g. atopic, contact or seborrhoeic dermatitis, eczema, psoriasis, acne, rosacea, post-peel, skin burning, itching, or IBD (inflammatory bowel disease). .

“Treatment” as used herein includes prevention, namely prophylactic as well as curative treatment.

Antibacterial activity is e.g. determined in vitro in the Agar Dilution Test according to National Committee for Clinical Laboratory Standards (NCCLS) 13 (1993) (No. 25), Document M7-A3, 3rd Edition, or Document M11-A3 for anaerobic bacteria.

Synergy is e.g. calculated as described in Berenbaum, Clin. Exp. Immunol. 28 (1977) 1, using an interaction term to correct for differences in mechanism between the two drugs, as described in Chou et al., Transpl. Proc. 26 (1994) 3043. The index of synergy is calculated as:

$$\frac{\text{dose of A}}{A_E} + \frac{\text{dose of B}}{B_E} + \frac{(\text{dose of A}) \times (\text{dose of B})}{A_E \times B_E}$$

in which the doses of the compounds A and B represent those used in a particular combination, and A_E and B_E are the individual doses of A and B respectively giving the same effect. If the result is less than 1, there is synergy; if the result is 1, the effect is additive; if the result is greater than 1, A and B are antagonistic. By plotting an isobologram of dose of A / A_E vs. dose of B / B_E the combination of maximum synergy can be determined. The synergistic ratio expressed in terms of the ratio by weight of the two compositions at synergistic amounts along the isobologram, especially at or near the point of maximum synergy, can then be used to determine formulations containing an optimally synergistic ratio of the two compounds.

Activity may e.g. be determined in known assay models for testing the individual components of the compositions.

Suitable animal assay models are e.g. as described in: Infect. Immunol. 44 (1992) 2636-2640; Antimicrob. Agents Chemother. 44 (2000) 255-260; JAC 42 (1998) 257-260; JAC 49 (2002) 455-465; and Infect. Immunol. 68 (2000) 2880-2887.

The invention also provides products and methods for co-administration of a macrolide T-cell immunomodulator or immunosuppressant, e.g. pimecrolimus or 5,6-dehydroascomycin, and an antibacterial, e.g. ciprofloxacin or erythromycin, at high compatible or synergistically effective dosages, e.g.:

- a method of treatment or prevention of diseases involving a bacterial or suspected or anticipated bacterial infection, or a method for immunomodulation or immunosuppression in a condition in which bacterial or suspected or anticipated bacterial colonization plays a role or in situations of bacterial resistance, in a subject suffering from or at risk for such infection or condition, comprising co-administering high compatible or synergistically effective amounts of a composition of the invention;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a medicament for co-administration in synergistically effective amounts with an antibacterial;
- the use of an antibacterial in the manufacture of a medicament for co-administration in synergistically effective amounts with a macrolide T-cell immunomodulator or immunosuppressant;
- a kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial in separate unit dosage forms, preferably wherein the unit dosage forms are suitable for administration of the component compounds in synergistically effective amounts, together with instruction for use, optionally with further means for facilitating compliance with the administration of the component compounds, e.g. a label or drawings;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with an antibacterial;
- the use of an antibacterial in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a macrolide T-cell immunomodulator or immunosuppressant;

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- a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial as a combined pharmaceutical preparation for simultaneous, separate or sequential use, preferably in synergistically effective amounts, e.g. for the treatment or prevention of a bacterial infection, or for immunomodulation or immunosuppression in a condition in which bacterial or suspected or anticipated bacterial colonization plays a role;
- a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with an antibacterial, e.g. in synergistically effective amounts, together with at least one pharmaceutically acceptable diluent or carrier, e.g. for use in treatment or prevention of a bacterial infection, or for immunomodulation or immunosuppression in a condition in which bacterial or suspected or anticipated bacterial colonization plays a role, or in a situation of bacterial resistance; and
- a process for the preparation of a composition of the invention comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

By “synergistically effective amounts” is meant an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of antibacterial which are individually below their respective effective dosages for a relevant indication, but which are pharmaceutically active on co-administration, e.g. in a synergistic ratio, for example as calculated above. Furthermore, “synergistically effective amounts” may mean an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of antibacterial which are individually equal to their respective effective dosages for a relevant indication, and which result in a more than additive effect.

The molar amount of macrolide T-cell immunomodulator or immunosuppressant present is from roughly similar to, to significantly less than the amount of antibacterial, preferably half as much or less. Compatible or synergistic ratios of macrolide T-cell immunomodulator or immunosuppressant to antibacterial by weight are thus suitably from about 10:1 to about 1:50, preferably from about 5:1 to about 1:20, most preferably from about 1:1 to about 1:15, e.g. about 1:12.

The compositions of the invention can be administered as a free combination, or the drugs can be formulated into a fixed combination, which greatly enhances the convenience for the patient.

Absolute dosages of the compounds will vary depending on a number of factors, e.g. the individual, the route of administration, the desired duration, the rate of release of the active agent and the nature and severity of the condition to be treated. For example, the amount of active agents required and the release rate thereof may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

For example, in prevention and treatment of atopic dermatitis or acne, or bacterial or suspected or anticipated bacterial infection, an initial dosage of about 2-3 times the maintenance dosage is suitably administered, followed by a daily dosage of about 2-3 times the maintenance dosage for a period of from one to two weeks, and subsequently the dose is gradually tapered down at a rate of about 5 % per week to reach the maintenance dosage. In general, compatible or synergistically effective amounts of 33-epichloro-33-desoxyascomycin and antibacterial such as ciprofloxacin on oral administration for use in prevention and treatment of atopic dermatitis or acne or bacterial diseases in larger animals, e.g. man, are amounts of 33-epichloro-33-desoxy-ascomycin of up to about 2 mg/kg/day, e.g. from about 0.01 mg/kg/day to about 2 mg/kg/day, preferably about 0.5 mg/kg/day, in combination or co-administration with amounts of antibacterial such as ciprofloxacin of up to about 50 mg/kg/day, e.g. from about 0.25 mg/kg/day to about 50 mg/kg/day, preferably about 2.5 mg/kg/day, in a synergistic ratio, as described. Suitable unit dosage forms for oral co-administration of these compounds thus may contain on the order of from about 0.5 mg to about 100 mg, preferably about 3 mg to about 30 mg of 33-epichloro-33-desoxyascomycin, and from about 0.1 mg to about 10 mg, preferably about 1 mg to about 3 mg of antibacterial. The daily dosage for oral administration is preferably taken in a single dose, but may be spread out over two, three or four dosages per day. For i.v. administration, the effective dosage is lower than that required for oral administration, e.g. about one fifth the oral dosage.

By "co-administration" is meant administration of the components of the compositions of the invention together or at substantially the same time, e.g. within fifteen minutes or less, either in the same vehicle or in separate vehicles, so that upon oral

administration, for example, both compounds are present simultaneously in the gastrointestinal tract. Preferably, the compounds are administered as a fixed combination.

While the present invention primarily contemplates combination or association of just two pharmaceutically active components, it does not exclude the presence of further active agents, e.g. one further active agent, as far as they do not contradict the purpose of the present invention.

Preferred such further pharmaceutically active components for combination or association are **retinoids**.

A suitable retinoid is for example:

- acitretin [etretin; (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nona-tetraenoic acid; Soriatane^R];
 - β -carotene (Carotaben^R; provitamin A);
 - etretinate [(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester];
 - isotretinoin (Accutane^R; Roaccutane^R);
 - motretinide [Tasmaderm^R; (all-E)-N-ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide];
 - retinal (retinaldehyde; retinene; vitamin A aldehyde);
 - retinoic acid (vitamin A acid; tretinoin);
 - retinol (vitamin A; Retinol^R);
 - retinol palmitate;
 - tamibaroten;
 - adapalene (Lorac^R; Differin^R);
 - alitretinoin; or
 - tazarotene (Zorac^R; Tazorac^R; synthetic acetylenic retinoid);
- preferably etretinate, isotretinoin or tazarotene; especially isotretinoin or tazarotene.

The compositions of the invention include compositions suitable for administration by any conventional route, in particular compositions suitable for administration either enterally, for example, orally, e.g. in the form of solutions for drinking, tablets or capsules, or

parenterally, e.g. in the form of injectable solutions or suspensions; or topically, e.g. for the treatment of inflammatory or bacterial conditions of the skin or mucosae, e.g. in the form of a dermal cream, ointment, ear drops, mousse, shampoo, solution, lotion, gel, emulgel or like preparation, e.g. in a concentration of from about 0.1 % to about 4 % by weight of each component, especially in combination or association with penetration enhancing agents, as well as for application to the eye, e.g. in the form of an ocular cream, gel or eye-drop preparation, for treatment of inflammatory or bacterial or suspected or anticipated bacterial conditions of the lungs and airways, e.g. in the form of inhalable compositions, and for mucosal application, e.g. in the form of vaginal tablets.

The compositions of the invention are suitably emulsions, microemulsions, emulsion preconcentrates or microemulsion preconcentrates, or solid dispersions, especially water-in-oil microemulsion preconcentrates or oil-in-water microemulsions, comprising the macrolide T-cell immunomodulator or immunosuppressant and the antibacterial in a synergistic ratio.

The compositions of the invention can be prepared in conventional manner, e.g. by mixing a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

The active agent components may be in free form or pharmaceutically acceptable salt form as appropriate.

The following Examples illustrate the invention. The compounds are in free, i.e. neutral or base form unless specified otherwise.

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Example 1: Cream

Component	Amount (g)
33-Epichloro-33-desoxyascomycin	1.00
erythromycin	2.00
triglycerides, medium chain	15.00
oleyl alcohol	10.00
sodium cetylstearyl sulfate	1.00
cetyl alcohol	4.00
stearyl alcohol	4.00
glyceryl monostearate	2.00
benzyl alcohol	1.00
propylene glycol	5.00
citric acid	0.05
sodium hydroxide	*
water	ad 100.0
* amount required to adjust pH to 5.5	

The preparation follows the conventional manufacturing procedures for an emulsion. The drug substances are added to the heated homogeneous oily phase which contains triglycerides medium chain, oleyl alcohol, sodium cetylstearyl sulfate, cetyl alcohol, stearyl alcohol and glyceryl monostearate. In parallel, the water phase containing benzyl alcohol, propylene glycol, citric acid and sodium hydroxide is heated at the same temperature as the oily phase. The oily phase is added to the water phase and homogeneisation is performed. The resultant cream is cooled to room temperature.

Example 2: Lotion

Component	Amount (g)
33-Epichloro-33-desoxyascomycin	1.00
erythromycin	2.00
propylene glycol	40.00
oleyl alcohol	5.00
isopropanol	<u>52.00</u>
total	100.00

Claims:

1. A pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with an antibacterial, together with at least one pharmaceutically acceptable diluent or carrier.
2. A composition according to claim 1 comprising 33-epichloro-33-desoxyascomycin in combination or association with sulfasalazin, ciprofloxacin, ofloxacin, erythromycin or gentamycin.
3. A method of treatment of a disease involving bacterial or suspected or anticipated bacterial infection, or a method for immunomodulation or immunosuppression in a condition in which bacterial or suspected or anticipated bacterial colonization plays a role or in a situation of bacterial resistance, in a subject suffering from or at risk for such infection or condition, comprising co-administering a high compatible or synergistically effective amount of a composition according to claim 1.
4. A process for the preparation of a composition according to claim 1 comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial, in combination or association with at least one pharmaceutically acceptable diluent or carrier.
5. A kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and an antibacterial in separate unit dosage forms, together with instructions for use.
6. A composition according to claim 1 or 2 comprising a further pharmaceutically active agent which is a retinoid.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/098376 A (FISHER GARY J ; UNIV MICHIGAN (US); KANG SEWON (US); VOORHEES JOHN J () 12 December 2002 (2002-12-12) page 3, last paragraph - page 4, line 5 page 5, paragraph 3 - page 6, paragraph 2 page 8, paragraph 2 claim 1	1-6
X	US 2003/021816 A1 (FISHER GARY J ET AL) 30 January 2003 (2003-01-30) page 1, paragraph 8 - paragraph 9 page 2, paragraphs 16-18,20 page 3, paragraph 24 claim 1	1-6
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

23 June 2004

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/003510

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 02/089796 A (MOORE HENRIETTA DENISE ; CORDIER ANDRE (CH); NOVARTIS AG (CH); KEHREN) 14 November 2002 (2002-11-14) page 13; table 3 page 15, paragraph 4 page 16, last paragraph - page 17, line 3 -----	1-6
P,X	WO 03/092702 A (MOSKOWITZ ROLAND W ; UNIV CLEVELAND HOSPITALS (US)) 13 November 2003 (2003-11-13) page 2, line 22 page 4, line 18 - line 23 -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/003510

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