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(54) Use of rapamycin for the manufacture of a medicament for the treatment of immunoinflammatory diseases

Verwendung von Rapamycin zur Herstellung eines Arzneimittels zur Behandlung von immunoinflammatorischen Krankheiten

Utilisation de rapamycine pour la fabrication d'un médicament pour le traitement de maladies immunoinflammatoires

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- **Antibiotics, vol. 37, no. 10, (1984), pages 1231-1237**

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Description

This invention relates to the use of rapamycin for the manufacture of a medicament for the tretment of immunoinflammatory disease.

Skin diseases such as contact hypersensitivity, atopic dermatitis, and psoriasis are characterised by hyperproliferative and inflammatory skin disorders. A large population suffers from these disorders, psoriasis; for example, afflicts approximately 2% of the population in Western countries [Ziboh, V.A. Psoriasis: Hyperproliferative/Inflammatory skin disorder, Drug Development Research 13: 137-146, (1988)]. Human skin diseases like psoriasis are characterised by histopathologically distinct patterns of infiltration by T cells, B cells, monocytes and granulocytes. These leukocyte cell infiltrations are the consequence of expression of intercellular adhesion molecules and release of cytokine and chemotactic factors by nonhematopoietically derived cells (e.g. keratinocytes) of the skin which in turn augment hyperplasia.

Current treatment of immunologically mediated skin disorders involves the use of antiinflammatory agents such as glucocorticoids and antiproliferative agents such as methotrexate, 5-fluorouracil, and retinoids. Recently, use of the immunosuppressive agent cyclosporin A has been reported to give clinical improvement of psoriasis [Ellis, J. Am. Med. Assoc. 256: 3110-3116, (1986)]. However, its usefulness in psoriasis is limited due to high incidence of nephrotoxicity [Ellis, New England J. Med. 324: 277-84, (1991)], and the observation of relapse after cessation of the treatment with cyclosporin A [Griffiths, J. Am. Acad. Dermatol. 23: 1242-1247, (1990)].

Rapamycin, a macrocyclic triene antibiotic produced by Streptomyces hygroscopicus [US Patent 3,929,992] has been shown to prevent the formation of humoral (IgE-like) antibodies in response to an albumin allergic challenge [Martel, R., Can. J. Physiol. Pharm. 55:48 (1977)], inhibit murine T-cell activation [Staruch, M., FASEB 3: 3411 (1989)], and prolong survival time of organ grafts in histoincompatible rodents [Morris, R., Med. Sci. Res. 17: 877 (1989)].

WO-A-9202229 published 20 February 1992 discloses compositions useful in treating inflammatory bowel disease comprising a non-specific suppressor cell inducing compound and a non-NS suppressor cell immunosuppressive compound which may be rapamycin and a pharmaceutical carrier.

US-A-5023263 describes 42-oxo-rapamycin and pharmaceutically acceptable salts thereof and their usefulness for the treatment of inflammatory skin or bowel disease.

This invention provides rapamycin for use in the preparation of a medicament for treating immunoinflammatory skin or bowel disease in a mammal. The medicament may be administered orally, parenterally, intranasally, intrabronchially, topically, transdermally, or rectally. In particular, rapamycin is useful in providing symptomatic relief of, preventing the progression of, or eradicating inflammatory skin, and bowel diseases. As such, rapamycin is useful in treating skin diseases such as psoriasis, atopic dermatitis, contact dermatitis, exczematous dermatisis, seborrheic dermatitis, Lichen planus, Pemphigus, bulus pemphigoid, Epidermolysis bullosa, urticaria, angiodemas, vasculitides, erythmas, cutaneous eosinphilias, and the like; and bowel disease such as inflammatory bowel disease.

The effect of rapamycin on skin and bowel diseases was established in two in vivo standard animal pharmacological test procedures emulating skin and bowel immunoinflammatory diseases observed in mammals. The procedures used and results obtained are described below.

The first in vivo standard pharmacological test procedure measured the effect of rapamycin on dermal inflammation, as measured by the prevention of tetradecanoylphorbol acetate (TPA) induced ear edema in Webster mice. Cyclophosphamide, cyclosporin (CsA), indomethacin, and BW755C also were evaluated for the purpose of comparison. The following briefly describes the procedure used.

Ferraile Swiss Webster mice (Buckshire; 8 weeks old) were divided into groups of six. Tetradecanoylphorbol acetate (TPA) were dissolved in acetone at concentrations of 200 μg/ml. Each mouse received 4 μg/ear of TPA on the right ear. These suboptimal doses of phlogistics were applied by an automatic pipette in 10 μl volumes to both the inner and outer surfaces of the ear. The left (control) received acetone or vehicle. Drugs were applied topically in acetone and in some cases 95% ethanol was used to solubilize the drug prior to dilution with acetone. Topical drug regimen was as follows: drugs were given 30 min. after treatment with TPA. Edema measurements were taken with an Oditest calipers. The thickness of the right and left ears were usually measured in units of 0.01 mm 4 h after TPA application. Ear edema was calculated by subtracting the thickness of the left ear (vehicle control) from right ear (treated ear).

The results obtained in the TPA induced ear edema standard pharmacological test procedure are shown in the following table.

Treatment Group	Dose (mg/ear)	Mean Edema (mm^2±SEM)	Percent Change
Control		28.3±1.1	--
Rapamycin	0.25	17.8±4.1	-37.1*
Rapamycin	1.0	12.0±2.5	-57.6*
Cyclophosphamide	0.25	16.5±3.1	-41.7*
Cyclophosphamide	1.0	15.0±2.4	-47.0*
Cyclosporin A	0.25	23.8±2.0	-15.9
Cyclosporin A	1.0	26.0±1.3	-7.1
Indomethacin	0.5	12.0±2.3	-57.6*
BW755C	0.5	12.0±2.4	-57.6*
BW755C	1.0	12.7±1.4	-55.1*

*Statistically significant ($p \leq 0.05$) difference from control mice.

The results of this standard pharmacological test procedure showed that rapamycin significantly ($p \leq 0.05$) prevented an acute inflammatory response following topical TPA administration. Cyclosporin A, an immunosuppressive agent typically compared with rapamycin, prevented the inflammatory response to a much lesser extent.

The second in vivo standard pharmacological test procedure measured the effect of rapamycin on preventing oxazalone-induced contact hypersensitivity of the mouse ear. This test procedure emulates the inflammatory response observed in immunoinflammatory diseases of the skin, and bowel in mammals. The following briefly describes the procedure used and results obtained. Dexamethasone, and cyclosporin A also were evaluated for the purpose of comparison.

Female, Swiss Webster mice (8 weeks old) were placed into groups of 6 and the abdominal area of each was shaved. The mice were sensitized to oxazolone (4-ethoxymethylene-2-phenyl-oxazol-5-one) by applying 100 µl of a 2% solution in 95% alcohol directly onto the shaved abdomen using an automatic pipette and rubbing the residual oxazolone into the skin with a round wooden stick. Six days after sensitization, each mouse was challenged by applying 20 µl of a 2% oxazolone solution in 95% alcohol to the right ear (10 µl on each side) and 20 µl of alcohol alone to the left ear. Compounds for topical applications were prepared in acetone and administered to the right ear 30 min. after challenge; acetone (vehicle) was applied to the left ear. Compounds for oral administration were suspended in 0.5 ml of 0.5% methyl cellulose and given ten min. prior to challenge. Ear thickness of both ears were measured in (mm x 10^{-2}) at 24 and 48 h after challenge using an Oditest caliper. Edema was calculated by subtracting the left ear thickness from the right ear thickness. Drug effects were determined by calculating the percentage change from control for each time period. The following results were obtained.

Compound	Dose	Route	Edema (mm x 10^{-2}±SE)	Percent Change
Control			34.7±2.9	
Unsensitized			4.2±1.3	
Rapamycin	20 mg/kg	p.o.	26.8±5.6	-22.6
Rapamycin	0.5 mg/ear	topical	9.7±3.4	-72.1*
Cyclosporin A	50 mg/kg	p.o.	27.5±3.9	-20.7
Cyclosporin A	1.0 mg/ear	topical	4.7±1.5	-86.5*
Dexamethasone	1 mg/kg	p.o.	25.8±4.2	-25.5
Dexamethasone	0.1 mg/ear	topical	1.2±0.4	-96.6*

The results of this in vivo standard pharmacological test procedure emulating immunoinflammatory diseases of the skin and bowel showed that rapamycin prevented the inflammatory changes in response to oxazalone-induced inflammation. Similar results were observed with dexamethasone and cyclosporin A.

In summary, the results of these standard pharmacological test procedures demonstrate that rapamycin is useful in treating immunoinflammatory skin and bowel disorders in a mammal. As such, rapamycin is useful in treating skin diseases such as psoriasis, atopic dermatitis, contact dermatitis, exczematous dermatitis, seborrheic dermatitis, Lichen planus, Pemphigus, bulus pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythmas, cutaneous eosinphilias, and the like; and bowel diseases such as inflammatory bowel disease.

Rapamycin has been shown to act synergistically with cyclosporin A both in vitro and in vivo. For example, Kahan has shown that rapamycin significantly augmented the inhibitory effects of cyclosporin A upon human peripheral lymphocyte activation by phytohemagglutinin, anti-CD_3 monoclonal antibody, and mixed lymphocyte reaction. Cyclosporin A potentiated the effect of rapamycin upon proliferation of IL-2 and IL-6 lymphokine-dependent cell lines. Additionally, the rapamycin/cyclosporin combination exerted immunosuppression of rejection reactions in rats toward heterotopic cardiac allografts, using concentrations at which each was individually ineffective. [Transplantation, 51: 232 (1991)]. As such, rapamycin can also be used in combination with cyclosporin A for the treatment of skin diseases such as psoriasis, atopic dermatitis, contact dermatitis, exczematous dermatitis, seborrheic dermatitis, Lichen planus, Pemphigus, bulus pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythmas, cutaneous eosinphilias, and the like; and bowel diseases such as inflammatory bowel disease.

When rapamycin is employed alone or in combination with cyclosporin A in the treatment of immunoinflammatory skin, and bowel diseases, it can be formulated neat or with a pharmaceutical carrier to a mammal in need thereof. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristare. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellent.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be adminisrered orally either in liquid or solid composition form.

Rapamycin, alone or in combination with cyclosporin A, may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermiable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Rapamycin, alone or in combination with cyclosporin A, may be administered topically as a solution, cream, or lotion by formulation with pharmaceutically acceptable vehicles containing 0.1 - 5 percent, preferably 2%, of active compound.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity

of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedure, projected daily dosages of active compound (either being rapamycin alone or in combination with cyclosporin A) would be 0.001 - 100 mg/kg, preferably between 0.1 - 50 mg/kg, and more preferably between 0.3 - 25 mg/kg. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. In general, rapamycin is most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

1. Use of rapamycin in the manufacture of a medicament for use in treating immunoinflammatory skin or bowel disease in a mammal providing that the medicament for use in treating immunoinflammatory bowel disease does not contain a non-specific suppressor cell inducing compound.

2. A use according to Claim 1 in which rapamycin is administered in combination with cyclosporin A.

3. A use according to Claim 1 or Claim 2 in which the medicament is a adapted for administration orally, parenterally, intranasally, intrabronchially, topically, transdermally or rectally.

4. A use according to any one of Claims 1 to 3 in which the skin disease is psoriasis, atopic dermatitis, contact dermatitis, exczematous dermatitis, seborrheic dermatitis, Lichen planus, Phemphigus, bulus pemphigoid, Epidermolysis bullosa, urticaria, angiodema, vasculitide, erythma or cutaneous eosinphilia.

5. A use according to any one of Claims 1 to 3 in which the medicament is for use in providing symptomatic relief of, preventing the progression of, or eradicating immunoinflammatory skin or bowel disease.

6. A use as claimed in any one of Claims 1 to 5 in which the medicament is in unit dosage form.

7. A use according to Claim 6 in which the unit dose comprises 0.001 to 100 mg/kg of rapamycin based on the weight of the mammal to be treated.

8. A use according to Claim 6 in which the unit dose comprises 0.1 to 50 mg/kg of rapamycin based on the weight of the mammal to be treated.

9. A use according to Claim 6 in which the unit dose comprises 0.3 to 25 mg/kg of rapamycin based on the weight of the mammal to be treated.

Claims for the following Contracting States : IE, PT

1. Use of rapamycin in the manufacture of a medicament for use in treating immunoinflammatory skin or bowel disease in a mammal.

2. A use according to Claim 1 in which rapamycin is administered in combination with cyclosporin A.

3. A use according to Claim 1 or Claim 2 in which the medicament is a adapted for administration orally, parenterally, intranasally, intrabronchially, topically, transdermally or rectally.

4. A use according to any one of Claims 1 to 3 in which the skin disease is psoriasis, atopic dermatitis, contact dermatitis, exczematous dermatitis, seborrheic dermatitis, Lichen planus, Phemphigus, bulus pemphigoid, Epidermolysis bullosa, urticaria, angiodema, vasculitide, erythma or cutaneous eosinphilia.

5. A use according to any one of Claims 1 to 3 in which the medicament is for use in providing symptomatic relief of, preventing the progression of, or eradicating immunoinflammatory skin or bowel disease.

6. A use as claimed in any one of Claims 1 to 5 in which the medicament is in unit dosage form.

7. A use according to Claim 6 in which the unit dose comprises 0.001 to 100 mg/kg of rapamycin based on the weight of the mammal to be treated.

8. A use according to Claim 6 in which the unit dose comprises 0.1 to 50 mg/kg of rapamycin based on the weight of the mammal to be treated.

9. A use according to Claim 6 in which the unit dose comprises 0.3 to 25 mg/kg of rapamycin based on the weight of the mammal to be treated.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

1. Verwendung von Rapamycin bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung immunentzündlicher Haut- oder Darmerkrankungen bei einem Säuger, mit der Maßgabe, daß das Medikament zur Verwendung bei der Behandlung immunentzündlicher Darmerkrankungen keine nicht-spezifische Suppressor-Zellen induzierende Verbindung enthält.

2. Verwendung nach Anspruch 1, wobei Rapamycin in Kombination mit Cyclosporin A verabreicht wird.

3. Verwendung nach Anspruch 1 oder 2, wobei das Medikament zur oralen, parenteralen, intranasalen, intrabronchialen, topischen, transdermalen oder rektalen Verabreichung geeignet ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Hauterkrankung Psoriasis, atopische Dermatitis, Kontaktdermatitis, ekzematöse Dermatitis, seborrhoische Dermatitis, Lichen planus, Pemphigus, bullöses Pemphigoid, Epidermolysis bullosa, Urtikaria, Angioödem, Vaskulitis, Erythem oder kutane Eosinophilie ist.

5. Verwendung nach einem der Ansprüche 1 bis 3, wobei das Medikament zur Verwendung beim Vorsehen symptomatischer Linderung, bei der Prävention der Progression oder Eradikation immunentzündlicher Haut- oder Darmerkrankungen ist.

6. Verwendung nach einem der Ansprüche 1 bis 5, wobei das Medikament in Einheitsdosierungsform vorliegt.

7. Verwendung nach Anspruch 6, wobei die Einheitsdosis 0,001 bis 100 mg/kg Rapamycin, bezogen auf das Gewicht des zu behandelnden Säugers, umfaßt.

8. Verwendung nach Anspruch 6, wobei die Einheitsdosis 0,1 bis 50 mg/kg Rapamycin, bezogen auf das Gewicht des zu behandelnden Säugers, umfaßt.

9. Verwendung nach Anspruch 6, wobei die Einheitsdosis 0,3 bis 25 mg/kg Rapamycin, bezogen auf das Gewicht des zu behandelnden Säugers, umfaßt.

Patentansprüche für folgende Vertragsstaaten : IE, PT

1. Verwendung von Rapamycin bei der Herstellung eines Medikaments zur Verwendung bei der Behandlung immunentzündlicher Haut- oder Darmerkrankungen bei einem Säuger.

2. Verwendung nach Anspruch 1, wobei Rapamycin in Kombination mit Cyclosporin A verabreicht wird.

3. Verwendung nach Anspruch 1 oder 2, wobei das Medikament zur oralen, parenteralen, intranasalen, intrabronchialen, topischen, transdermalen oder rektalen Verabreichung geeignet ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, wobei die Hauterkrankung Psoriasis, atopische Dermatitis, Kontaktdermatitis, ekzematöse Dermatitis, seborrhoische Dermatitis, Lichen planus, Pemphigus, bullöses Pemphigoid, Epidermolysis bullosa, Urtikaria, Angioödem, Vaskulitis, Erythem oder kutane Eosinophilie ist.

5. Verwendung nach einem der Ansprüche 1 bis 3, wobei das Medikament zur Verwendung beim Vorsehen sympto-

matischer Linderung, bei der Prävention der Progression oder Eradikation immunentzündlicher Haut- oder Darmerkrankungen ist.

6. Verwendung nach einem der Ansprüche 1 bis 5, wobei das Medikament in Einheitsdosierungsform vorliegt.

7. Verwendung nach Anspruch 6, wobei die Einheitsdosis 0,001 bis 100 mg/kg Rapamycin, bezogen auf das Gewicht des zu behandelnden Säugers, umfaßt.

8. Verwendung nach Anspruch 6, wobei die Einheitsdosis 0,1 bis 50 mg/kg Rapamycin, bezogen auf das Gewicht des zu behandelnden Säugers, umfaßt.

9. Verwendung nach Anspruch 6, wobei die Einheitsdosis 0,3 bis 25 mg/kg Rapamycin, bezogen auf das Gewicht des zu behandelnden Säugers, umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE

1. Utilisation de la rapamycine dans la fabrication d'un médicament pour l'utilisation dans le traitement de maladie immunoinflammatoire de la peau ou de l'intestin chez un mammifère, pourvu que le médicament pour l'utilisation dans le traitement de maladie immunoinflammatoire de l'intestin ne contient pas un constituant non spécifique inducteur de cellule suppresseur.

2. Utilisation suivant la revendication 1, dans laquelle la rapamycine est administrée en combinaison avec la cyclosporine A.

3. Utilisation suivant la revendication 1 ou la revendication 2, dans laquelle le médicament est adapté pour l'administration orale, parentérale, intranasale, intrabronchique, topique, transdermique ou rectale.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle la maladie de la peau est le psoriasis, la dermatite atopique, la dermatite de contact, la dermatite exczémateuse, la dermatite séborrhéique, le lichen plan, le pemphigus, la pemphigoïde bulleuse, l'épidermolyse bulleuse, l'urticaire, l'angiodermite, la vasculite, l'érythème, l'éosinophilie cutanée.

5. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle le médicament est à utiliser pour fournir un soulagement symptomatique, en prévenant la progression ou en éradiquant, la maladie immunoinflammatoire de la peau ou de l'intestin.

6. Utilisation suivant l'une quelconque des revendications 1 à 5, dans laquelle le médicament est sous forme de dosage unitaire.

7. Utilisation suivant la revendication 6, dans laquelle la dose unitaire comprend 0,001 à 100 mg par kg de rapamycine sur base du poids du mammifère à traiter.

8. Utilisation suivant la revendication 6, dans laquelle la dose unitaire comprend 0,1 à 50 mg par kg de rapamycine sur base du poids du mammifère à traiter.

9. Utilisation suivant la revendication 6, dans laquelle la dose unitaire comprend 0,3 à 25 mg par kg de rapamycine sur base du poids du mammifère à traiter.

Revendications pour les Etats contractants suivants : IE, PT

1. Utilisation de la rapamycine dans la fabrication d'un médicament pour l'utilisation dans le traitement de maladie immunoinflammatoire de la peau ou de l'intestin chez un mammifère.

2. Utilisation suivant la revendication 1, dans laquelle la rapamycine est administrée en combinaison avec la cyclosporine A.

3. Utilisation suivant la revendication 1 ou la revendication 2, dans laquelle le médicament est adapté pour l'adminis-

tration orale, parentérale, intranasale, intrabronchique, topique, transdermique ou rectale.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle la maladie de la peau est le psoriasis, la dermatite atopique, la dermatite de contact, la dermatite exczémateuse, la dermatite séborrhéique, le lichen plan, le pemphigus, la pemphigoïde bulleuse, l'épidermolyse bulleuse, l'urticaire, l'angiodermite, la vasculite, l'érythème, l'éosinophilie cutanée.

5. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle le médicament est à utiliser pour fournir un soulagement symptomatique, en prévenant la progression ou en éradiquant, la maladie immunoinflammatoire de la peau ou de l'intestin.

6. Utilisation suivant l'une quelconque des revendications 1 à 5, dans laquelle le médicament est sous forme de dosage unitaire.

7. Utilisation suivant la revendication 6, dans laquelle la dose unitaire comprend 0,001 à 100 mg par kg de rapamycine sur base du poids du mammifère à traiter.

8. Utilisation suivant la revendication 6, dans laquelle la dose unitaire comprend 0,1 à 50 mg par kg de rapamycine sur base du poids du mammifère à traiter.

9. Utilisation suivant la revendication 6, dans laquelle la dose unitaire comprend 0,3 à 25 mg par kg de rapamycine sur base du poids du mammifère à traiter.

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Title USE OF RAPAMYCIN FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF IMMUNOINFLAMMATORY DISEASES.

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