patent, col 11 lines 52-61) and other chronic inflammatory and allergen-induced dermatoses. For treatment of such dermatoses, roflumilast emulsions, suspensions, gels or solutions for topical application have been described (‘298 patent, col 12, lines 37-64).

Topical application of potent pharmacological agents like roflumilast for treating skin diseases has been found to provide superior delivery, lower systemic exposure and greater ease of use for patients. The molecular structure of the compound ultimately dictates the ability of the drug to cross the epithelium of the tissue to which the product is applied. For topical application to skin, selection of the components of the formulation dictates the maximum skin permeation that the formulator can achieve. Creams, lotions, gels, ointments and foams are just a few of the more familiar forms of topical products that contain active pharmaceutical ingredients (API) for application to the skin.

SUMMARY ~~OF THE INVENTION~~

In accordance with the present disclosure ~~invention~~, it has been discovered that topically administered roflumilast exhibits anti-fungal properties, in addition to its known anti-inflammatory properties as a PDE4 inhibitor. These characteristics make topical roflumilast an optimal treatment method for treating fungal infections, fungal overgrowth of hair, skin or nails and inflammation due to fungal hypersensitivity. Topical roflumilast has exhibited significant and fast reduction of the *Malassezia* fungus and a high seborrheic dermatitis treatment success rate, with an Investigator Global Assessment Success rate at week 8 for 0.3% roflumilast of 73.8% compared to a vehicle foam rate of 40.9%. The quick and successful treatment results indicate

that topically administered roflumilast is an effective antifungal agent and presents a viable alternative to current antifungal treatments.

In one aspect, there is provided use of a composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection in a subject in need thereof, wherein the fungal infection is caused by *Malassezia spp.*

In another aspect, there is provided use of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection, fungal overgrowth and/or hypersensitivity to *Malassezia spp* in a subject in need thereof, wherein said roflumilast or pharmaceutically acceptable salt thereof is to be topically administered to the subject, and wherein the fungal infection or overgrowth is caused by *Malassezia spp*.

In another aspect, there is provided use of a composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection or overgrowth in a subject in need thereof, wherein said roflumilast or pharmaceutically acceptable salt thereof is to be topically administered to the subject, wherein the subject is suffering from seborrheic dermatitis, and wherein the fungal infection or overgrowth is caused by *Malassezia* species.

In another aspect, there is provided use of a composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection, overgrowth and/or hypersensitivity in a subject suffering from seborrheic dermatitis, wherein said

roflumilast or pharmaceutically acceptable salt thereof is to be topically administered to the subject, and wherein the fungal infection, overgrowth and/or hypersensitivity is caused by *Malassezia* species.

In another aspect, there is provided use of a foam composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection or overgrowth in a human suffering from seborrheic dermatitis, wherein said foam composition is to be topically administered to the human, wherein the fungal infection or overgrowth is caused by *Malassezia furfur* and wherein said antifungal effective amount of roflumilast is 0.3% w/w.

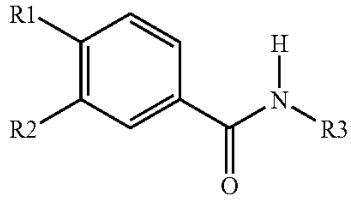
In another aspect, there is provided use of a composition comprising an antifungal effective amount of roflumilast in the manufacture of a medicament for reducing a count of at least one *Malassezia* species in a patient suffering from seborrheic dermatitis, wherein said composition is to be topically administered.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the results of an in vitro micro-dilution susceptibility assay for testing the anti-fungal activity of roflumilast. As shown in Figure 1 and Table B roflumilast has been shown to have antifungal activity against Malassezia species.

DETAILED DESCRIPTION OF THE INVENTION

Roflumilast is a compound of the formula (I)



(I)

wherein R1 is difluoromethoxy, R2 is cyclopropylmethoxy and R3 is 3,5-dichloropyrid-4-yl.

This compound has the chemical name N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamid- e (INN: roflumilast).

Hexylene glycol (PharmaGrade. USP/NF) is 2-methyl-2,4-pentanediol of the formula (II).

CLAIMS

1. Use of a composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of ~~A method of treating~~ a fungal infection in a subject in need thereof, ~~comprising administering to the subject a therapeutically effective amount of roflumilast or a pharmaceutically acceptable salt thereof,~~ wherein the fungal infection is caused by *Malassezia spp*.

2. The ~~method~~ use according to claim 1, wherein said roflumilast is to be administered topically.

3. The use ~~method~~ according to claim 1, wherein said *Malassezia spp.* is selected from the group consisting of *M. furfur, M. restricta, and M. globosa*, preferably *M. furfur*.

~~4. The method according to claim 3, wherein said *Malassezia spp.* is *M. furfur*.~~

~~5~~4. The use ~~method~~ according to claim 1, wherein the fungal infection comprises fungal overgrowth of hair, skin or nails.

~~65~~. The use ~~method~~ according to claim 1, wherein said subject is suffering from seborrheic dermatitis, dandruff, dupilumab facial redness, tinea versicolor, pityriasis versicolor, tinea circinata, tinea pedis, tinea unguium, tinea manus, tinea cruris, tinea corporis, tinea faciei, tinea capitis, or tinea incognito, preferably said subject is suffering from seborrheic dermatitis.

~~7. The method according to claim 6, wherein said subject is suffering from seborrheic dermatitis.~~

~~86~~. The use ~~method~~ according to claim 1, wherein said composition:

comprises carriers suitable for topical administration;

is selected from the group consisting of an aerosol, a foam, a spray, an emulsion, a gel, a liquid, an ointment, a paste, a shampoo, a suspension, and a system, preferably a foam;

comprises 0.3% w/w roflumilast; and/or

comprises roflumilast, white petrolatum, isopropyl palmitate, cetearyl alcohol, dicetyl phosphate, ceteth-10 phosphate, hexylene glycol, diethylene glycol monoethyl ether, methylparaben, propylparaben and water.

~~9. The method according to claim 1, wherein said composition is selected from the group consisting of an aerosol, a foam, a spray, an emulsion, a gel, a liquid, an ointment, a paste, a shampoo, a suspension, and a system.~~

~~10. The method according to claim 9, wherein said composition is a foam.~~

~~11. The method according to claim 1, wherein said composition comprises 0.3% w/w roflumilast.~~

~~12. The method according to claim 1, wherein said composition comprises roflumilast, white petrolatum, isopropyl palmitate, cetearyl alcohol, dicetyl phosphate, ceteth-10 phosphate, hexylene glycol, diethylene glycol monoethyl ether, methylparaben, propylparaben and water.~~

~~13~~7. The use ~~method~~ according to claim 1, wherein said composition consists of:

roflumilast	0.3% w/w
white petrolatum	10.0% w/w
isopropyl palmitate	5.0% w/w
cetearyl alcohol, dicetyl phosphate and ceteth-10 phosphate blend	10.0% w/w

hexylene glycol	2.0% w/w
diethylene glycol monoethyl ether	25.0% w/w
methylparaben	0.2% w/w
propylparaben	0.05% w/w, and
purified water	q.s. ad 100 (47.45%).

~~14~~8. The use ~~method~~ according to claim 1, further comprising ~~administering~~ an additional anti-fungal agent and/or an anti-inflammatory agent to be administered.

~~15~~9. The use ~~method~~ according to claim ~~14~~ 8 wherein said additional anti-fungal agent is selected from the group consisting of: drugs containing miconazole, ciclopirox olamine, clotrimazole, butenafine, terbinafine, amorolfine, naftifine, tolnaftate, ketoconazole, efinaconazole, griseofulvin, imidazoles, triazole, voriconazole, benzimidazole, ethylparaben, flucytosine, salicylic acid, selenium sulfide, and undecylenic acid and/or said additional anti-inflammatory agent is a corticosteroid or a calcineurin inhibitor.

~~16. The method according to claim 14 wherein said additional anti-inflammatory agent is a corticosteroid or a calcineurin inhibitor.~~

~~17. A method for reducing facial redness or inflammation due to a *Malassezia* infection, treatment of a *Malassezia* infection and/or *Malassezia* hypersensitivity, comprising topically administering an effective amount of roflumilast to a patient in need of such treatment.~~

~~18. The method according to claim 17, wherein said *Malassezia* hypersensitivity is due to treatment with dupilumab.~~

~~19. The method according to claim 17, wherein said roflumilast is administered in a composition which does not contain ethanol, isopropyl alcohol or denatured alcohol.~~

~~20. The method according to claim 19, wherein said composition comprises roflumilast, white petrolatum, isopropyl palmitate, cetearyl alcohol, dicetyl phosphate, ceteth-10 phosphate, hexylene glycol, diethylene glycol monoethyl ether, methylparaben, propylparaben and water.~~

~~21. The method according to claim 17, wherein said Malassezia hypersensitivity is caused by *M. furfur*, *M. restricta*, and/or *M. globosa*.~~

~~22. The method according to claim 17, further comprising administering an anti-inflammatory agent.~~

~~23~~10. Use of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of ~~A method of treating~~ a fungal infection, fungal overgrowth and/or hypersensitivity to *Malassezia spp* in a subject in need thereof, wherein said ~~comprising topically administering to the subject a therapeutically effective amount of~~ roflumilast or ~~a~~ pharmaceutically acceptable salt thereof is to be topically administered to the subject, and wherein the fungal infection or overgrowth is caused by *Malassezia spp*.

11. Use of a composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection or overgrowth in a subject in need thereof, wherein said roflumilast or pharmaceutically acceptable salt thereof is to be topically administered to the subject, wherein the subject is suffering from seborrheic dermatitis, and wherein the fungal infection or overgrowth is caused by *Malassezia* species.

12. The use according to claim 11, wherein said subject is a human.

13. The use according to claim 11, wherein said composition is a foam and/or comprises 0.3% w/w roflumilast.

14. The use according to claim 11 or 13, wherein said fungal infection is caused by fungi selected from the group consisting of *Malassezia furfur*, *Malassezia restricta*, and *Malassezia globosa*, preferably *Malassezia furfur*.

15. The use according to claim 11, wherein said composition further comprises a phosphate ester surfactant.

16. The use according to claim 15, wherein said phosphate ester surfactant:

comprises a blend of cetearyl alcohol, dicetyl phosphate, and ceteth-10 phosphate;

is in an amount between 1% to 25% w/w; and/or

is in an amount of 2% w/w.

17. The use according to claim 11, wherein said composition further comprises diethylene glycol monoethyl ether.

18. The use according to claim 17, wherein said diethylene glycol monoethyl ether is in an amount between 10% to 30% w/w or in an amount of 25% w/w.

19. The use according to claim 11, wherein said composition further comprises hexylene glycol.

20. The use according to claim 19, wherein said hexylene glycol is in an amount between 0.1% to 20% w/w, in an amount of 0.5% to 2% w/w, or in an amount of 2% w/w.

21. Use of a composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection, overgrowth and/or hypersensitivity in a subject suffering from seborrheic dermatitis, wherein said roflumilast or pharmaceutically acceptable salt thereof is to be topically administered to the subject, and wherein the fungal infection, overgrowth and/or hypersensitivity is caused by *Malassezia* species.

22. The use according to claim 21, wherein said subject is a human.

23. The use according to claim 21, wherein said composition is a foam and/or comprises 0.3% w/w roflumilast.

24. The use according to claim 21 or 23, wherein said fungal infection is caused by fungi selected from the group consisting of *Malassezia furfur*, *Malassezia restricta*, and *Malassezia globosa*, preferably *Malassezia furfur*.

25. Use of a foam composition comprising an antifungal effective amount of roflumilast or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a fungal infection or overgrowth in a human suffering from seborrheic dermatitis, wherein said foam composition is to be topically administered to the human, wherein the fungal infection or overgrowth is caused by *Malassezia furfur* and wherein said antifungal effective amount of roflumilast is 0.3% w/w.

26. The use according to claim 25, wherein said composition is a foam.

27. Use of a composition comprising an antifungal effective amount of roflumilast in the manufacture of a medicament for reducing a count of at least one *Malassezia* species in a patient suffering from seborrheic dermatitis, wherein said composition is to be topically administered.

28. The use according to claim 27, wherein said composition is a foam.

29. The use according to claim 28, wherein said composition further comprises a phosphate ester surfactant.

30. The use according to claim 29, wherein said phosphate ester surfactant:

comprises a blend of cetearyl alcohol, dicetyl phosphate, and ceteth-10 phosphate;

is in an amount between 1% to 25% w/w; and/or

is in an amount of 2% w/w.

31. The use according to claim 27, wherein said composition further comprises diethylene glycol monoethyl ether.

32. The use according to claim 31, wherein said diethylene glycol monoethyl ether is in an amount between 10% to 30% w/w or is in an amount of 25% w/w.

33. The use according to claim 27, wherein said composition further comprises hexylene glycol.

34. The use according to claim 27, wherein said Malassezia species is selected from the group consisting of *Malassezia furfur*, *Malassezia restricta*, and *Malassezia globosa*.

~~24. A method for reducing facial redness and inflammation caused by treatment of moderate to severe atopic dermatitis, comprising topically administering to a subject in need of such treatment, a therapeutically effective amount of roflumilast or a~~

~~pharmaceutically acceptable salt thereof, wherein said facial redness and inflammation is caused by a *Malassezia spp* infection.~~

~~25. The method according to claim 24, wherein said *Malassezia spp* infection was or is currently being treated with dupilumab.~~

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