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PATENT REQUEST : STANDARD PATENT

I/We, being the person(s) identified below as the Applicant(s), request the grant of a Standard Patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying complete specification.

Applicant(s) and
Nominated Person(s): DIOMED DEVELOPMENTS LIMITED

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Invention Title: COMPOSITIONS FOR THE TREATMENT OF
INFLAMMATORY PROLIFERATIVE SKIN DISEASE
AND THEIR USE

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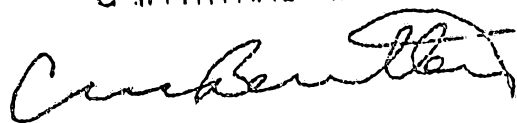
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BASIC CONVENTION APPLICATION DETAILS

Application No:	Country:	Application Date:
9313866.7	GB	05 July 1993

DATED: 30 June 1994
DIOMED DEVELOPMENTS LIMITED

GRIFFITH HACK & CO.



Patent Attorney for and
on behalf of the Applicant

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NOTICE OF ENTITLEMENT

I/We DIOMED DEVELOPMENTS LIMITED

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UNITED KINGDOM

being the applicant(s) in respect of an application for a patent for an invention entitled
COMPOSITIONS FOR THE TREATMENT OF INFLAMMATORY PROLIFERATIVE
SKIN DISEASE AND THEIR USE (Application No. 66089/94), state the following:

1. The nominated person(s) has/have, for the following reasons, gained entitlement from the actual inventor(s):

THE NOMINATED PERSON WOULD BE ENTITLED
TO HAVE ASSIGNED TO IT A PATENT GRANTED TO
THE INVENTOR IN RESPECT OF THE SAID
INVENTION.

2. The nominated person(s) has/have, for the following reasons, gained entitlement from the basic applicant(s) listed on the patent request:

THE APPLICANT AND NOMINATED PERSON IS THE
BASIC APPLICANT.

3. The basic application(s) listed on the request form is/are the first application(s) made in a Convention country in respect of the invention.

DATE: 21 October 1996

DIOMED DEVELOPMENTS LIMITED

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COMPOSITIONS FOR THE TREATMENT OF INFLAMMATORY PROLIFERATIVE SKIN DISEASE AND THEIR USE

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(56) Prior Art Documents
GB 981144
EP 0278660

(57) Claim

1. A method of treating an inflammatory skin disease which comprising applying thereto a composition comprising 8-hydroxyquinoline in free form dissolved in a pharmaceutically acceptable essentially anhydrous solvent.

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COMPLETE SPECIFICATION
STANDARD PATENT

Applicant:

DIOMED DEVELOPMENTS LIMITED

Invention Title:

COMPOSITIONS FOR THE TREATMENT OF
INFLAMMATORY PROLIFERATIVE SKIN DISEASE
AND THEIR USE

The following statement is a full description of this
invention, including the best method of performing it known
to me/us:

COMPOSITIONS FOR THE TREATMENT OF
INFLAMMATORY PROLIFERATIVE SKIN DISEASE AND THEIR USE

This invention relates to methods for the
5 topical treatment of inflammatory proliferative skin
diseases, especially psoriasis.

Psoriasis is associated with the rapid turnover
of skin cells (hyperproliferation) accompanied by a loss of
differentiation so that silvery white scales form on the
10 surface of the skin. Additionally, the capillaries become
tortuous and dilated and an inflammatory reaction occurs,
so that the skin reddens. The elevated silvery white
scales on a contrasting red background produce the
unsightly lesions characteristic of psoriasis.

15 A number of methods are used for the topical
treatment of psoriasis, but none is entirely satisfactory.
Historically, the earliest form of therapy involved the use
of coal tar derivatives. These are sometimes effective but
are extremely messy. Subsequently, the use of dithranol
20 (1,8-dihydroxy-9-anthrone) was developed. This substance
is very effective, but it causes irritation of the skin and
staining both of the skin and adjacent materials, which are
disadvantages especially in home treatment. Topical
corticosteroids have also been used. Although these are
25 clean and convenient to use, they are only suppressive in
action and therefore only provide short term relief of
symptoms. In addition, psoriasis treated with
corticosteroids tends to relapse in a more resistant form,



so that more aggressive therapy is later required.

The latest form of topical treatment of psoriasis is the use of synthetic Vitamin D derivatives. These derivatives are reasonably effective but have to be used in
5 extremely low concentrations in order to avoid systemic calcitropic effects. Thus, it has been shown that increasing the concentration of the derivative in the composition above 0.005% w/w is liable to cause an increase in plasma calcium levels and, even at the 0.005% w/w level
10 used in the marketed licensed product, there have been reports of increased plasma calcium levels. Such preparations moreover rarely clear the psoriasis, perhaps because of the very low strength used. Patients therefore have to continue treatment for extended periods which
15 increases the risk of systemic side effects. Furthermore, a significant proportion of patients experience irritation and this restricts usage, particularly on delicate areas of the skin such as the face. Although it is not known for certain, the Vitamin D appears to alter calcium metabolism
20 in the epidermal cells, which results in reduced cell proliferation and increased cell differentiation, leading to a correction of the abnormal pathophysiology of the epidermal cells and a return to normal skin growth and development.

25 We have now found that 8-hydroxyquinoline is effective in the treatment of psoriasis and other inflammatory proliferative skin diseases by topical application to the affected area of skin. More

particularly, we have found that 8-hydroxyquinoline at a concentration of 0.25% in a simple ointment or gel has a rapid ameliorating effect on patients with psoriasis. It rapidly removes the scales on resistant patches of
5 psoriasis, such as those which occur on the elbows and knees.

A possible explanation for the effectiveness of 8-hydroxyquinoline may be that it deprives the epidermal cells of the calcium they need for rapid proliferation by
10 chelating the calcium and thus rendering it unavailable. However other calcium chelating agents are not effective against psoriasis. For example ethylene diamine tetracetic acid and its salts were tested in various formulations and found to have no clinical effect whatsoever. Similarly,
15 other chelating agents, including penicillamine, glycine, dimercaprol, citric acid, and 5-chloro-7-iodo-8-hydroxyquinoline (the topical antiseptic sold under the registered Trade Mark "Vioform") were all found to have no beneficial effect in the topical treatment of psoriasis.

20 8-Hydroxyquinoline is a white or slightly off-white solid which is relatively insoluble in water but dissolves in many organic solvents. When dissolved in anhydrous ethanol at a concentration of 1% w/w, it produces a clear almost colourless solution. On addition of water, e.g. 20%
25 of the total volume, the 8-hydroxyquinoline remains in solution but the colour changes to yellow. This implies that 8-hydroxyquinoline exists in different forms, depending on whether or not water is present, viz a yellow

form in the presence of water and a colourless form under essentially anhydrous conditions.

Trials have been carried out with both aqueous systems (e.g. aqueous gels) and essentially anhydrous systems (e.g. ointments or anhydrous gels) and it has been found that only the essentially anhydrous systems are effective in the treatment of psoriasis. Small quantities of water, e.g. 3 to 4% by weight, can be present in the essentially anhydrous compositions without them becoming inactive, but the desired therapeutic effect is lost if more than a small amount of water is present. This loss of activity is associated with the development of the yellow colour shown by 8-hydroxyquinoline in the presence of water and the presence or absence of this yellow colour thus provides a convenient way of determining whether a composition contains too much water to be active. It is thus a very simple matter to determine by experiment how much water a particular formulation can tolerate before it becomes inactive.

Water is not the only substance capable of rendering 8-hydroxyquinoline unavailable and, in consequence, without useful therapeutic effect. More particularly, acids and bases render 8-hydroxyquinoline unavailable by either converting it into a salt or limiting its release by hydrogen bond formation. Also substances such as polyhydric alcohols, polyethylene glycol, polyethylene glycol ethers and esters and non-ionic surfactants in general prevent release of 8-hydroxyquinoline into the skin

from the phase containing it. The presence of such substances in the compositions of the invention must therefore be avoided. It is believed that all such substances which render 8-hydroxyquinoline therapeutically
5 unavailable have the property already noted of converting it into a yellow form, a colour change which is believed to be associated with disturbance of the intramolecular hydrogen bonding of the 8-hydroxyquinoline, believed to be a prerequisite for efficient dermatological availability.
10 The compositions of the invention are thus white (colourless) rather than yellow (unless a yellow colouring agent is added).

The present invention accordingly provides a method for the treatment of an inflammatory proliferative
15 skin disease which comprises applying thereto (i.e. skin affected by the disease) a composition comprising 8-hydroxyquinoline in free form dissolved in a pharmaceutically acceptable essentially anhydrous solvent. The expression "essentially anhydrous", as used herein,
20 means that the solvent (or phase where the composition has more than one phase) in which the 8-hydroxyquinoline is present is either completely anhydrous or contains insufficient water to produce a yellow colour in the solvent (or phase). Such compositions preferably comprise
25 from 0.01 to 5.0% by weight, more preferably from 0.1 to 1.0% by weight, most preferably 0.1 to 0.5% by weight, of 8-hydroxyquinoline. The essentially anhydrous solvent is preferably paraffin or another topically acceptable,



oleophilic, and water-immiscible solvent. A mixture of white soft paraffin and isopropyl myristate has the required properties and is preferred.

The pharmaceutical composition may further
5 comprise a lipid soluble antioxidant which is chemically inert towards 8-hydroxyquinoline to protect the 8-hydroxyquinoline from atmospheric oxidation.

The pharmaceutical compositions may also
comprise a topical corticosteroid, for example,
10 betamethasone valerate, hydrocortisone, or another corticosteroid known to be suitable for topical application, in an amount of 0.01 to 1.0% by weight. These compositions are useful for treating cases where there is excessive inflammation present.

15 These pharmaceutical compositions are preferably for use in the treatment of psoriasis.

Although the present invention is primarily concerned with the treatment of psoriasis, it is within the scope of the invention to use 8-hydroxyquinoline in the
20 treatment of other inflammatory skin conditions in which hyperproliferation or thickening occurs, e.g. chronic eczema/dermatitis.

While a simple ointment containing 8-hydroxyquinoline in white soft paraffin is (as noted
25 above) effective in the present invention, it is desirable to reduce the greasiness of the formulation while retaining the 8-hydroxyquinoline in an essentially anhydrous oleophilic environment. To achieve this objective, the



compositions of the invention may be provided in the form of an oil-in-water semi-solid emulsion, in which the 8-hydroxyquinoline is dissolved in the discontinuous oil phase. The aqueous phase of such compositions must have a substantially neutral pH to ensure that the partition of 8-hydroxyquinoline is strongly in favour of the oil phase; the aqueous phase, can, if desired, contain anionic dispersing agent. In these circumstances, even though the continuous phase is aqueous, the 8-hydroxyquinoline is present in an essentially anhydrous environment because of the very low solubility of water in the dispersed oily phase. Such a composition may contain over 50% of a dispersed oil phase in which the 8-hydroxyquinoline is dissolved. Although the lipid phase is preferably preponderantly white soft paraffin, chosen for its inertness and water immiscibility, a small amount of isopropyl myristate is preferably added to improve emolliency. In addition, since 8-hydroxyquinoline may be subject to atmospheric oxidation, a small concentration of an antioxidant, may be included. It is also preferable that the aqueous phase contains a preservative, preferably phenoxyethanol in an amount of 0 to 0.2% by weight. This is because the 8-hydroxyquinoline, which is itself an antiseptic, is held almost entirely in the lipid phase.

25 In an alternative embodiment of the invention, the 8-hydroxyquinoline is provided as a therapeutically active gel by dissolving in it in free form in an essentially anhydrous pharmaceutically acceptable solvent and gelling

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with a thickener. For example, ethanol may be used which forms a clear colourless gel on the addition of hydroxypropyl cellulose. A small proportion of a soluble inert lipid, such as isopropyl myristate may be added to
5 reduce the drying effect of the alcohol. Again, a small concentration of an antioxidant may be added. The amount of thickener to be added is adjusted to produce a final formulation varying from a slightly viscous liquid, for application as a lotion, to a semi-solid gel.

10 The following examples illustrate the invention.
Parts are by weight.

EXAMPLE 1

	Most Preferred Range	Range
8-hydroxyquinoline	0.1, 0.25, 0.5 or 1.0	0.01 - 5.0
White Soft Paraffin BP	40.0	10 - 50
Isopropyl Myristate BP	10.0	0 - 30
Cetostearyl Alcohol BP	7.0	5 - 10
Sodium Lauryl Sulphate BP	1.0	0.5 - 2.0
Phenoxyethanol BP	0.1	0 - 0.2
Purified Water BP to	100.0	

The formulation is made as follows:

1. Melt together the White Soft Paraffin (40 parts), isopropyl myristate (10 parts) and Cetostearyl Alcohol (7 parts) by heating to 70°C.
2. Dissolve 8-hydroxyquinoline (0.5 parts) in the heated oily phase so obtained.
3. Boil water (41.35 parts) thoroughly to remove any dissolved oxygen and allow to cool to 70°C.
4. Dissolve Sodium Lauryl Sulphate (1 part) and Phenoxyethanol (0.1 part) in the water at 70°C.
5. Add the aqueous phase so obtained to the oily phase and homogenise continuously, avoiding aeration, allowing the mixture to cool until semi-solid, to produce an almost white cream.
6. Pack into aluminium collapsible tubes.

15 EXAMPLE 2

	Most Preferred Range	Range
8-hydroxyquinoline	0.1, 0.25, 0.5 or 1.0	0.01 - 2.0
Isopropyl myristate BP	10.0	5 - 15
Hydroxypropyl Cellulose* BP	3.0	0.5 - 3.5
Ethanol BP to	100.0	

* - Klucel HF, Aqualon

The formulation is made as follows:

1. Dissolve the 8-hydroxyquinoline in the alcohol.
2. Add the isopropyl myristate and mix well.
- 5 3. Warm to 50-60°C.
4. Add the hydroxypropyl cellulose slowly with continuous mixing, avoiding aeration.
5. Allow to cool with occasional mixing to form a clear colourless gel.
- 10 6. Pack into a bottle or aluminium tube depending on the viscosity.

The preparation should be applied twice daily to the affected areas of psoriasis. For thin areas of psoriasis a concentration of 0.1% to 0.5% 8-hydroxyquinoline may be
15 sufficient, while for the thicker areas a concentration of 0.5% or 1.0% 8-hydroxyquinoline may be required. The preparation is non-irritant, it produces no staining, and has no effect on systemic calcium levels. It has been shown to be at least as effective as Vitamin D derivatives
20 in some subjects, and even more effective in others. 8-hydroxyquinoline is particularly useful in the treatment of resistant areas of psoriasis which may have to be treated for extended periods.

If desired, betamethasone valerate may be
25 incorporated in the above formulations in a concentration of 0.1% by weight.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating an inflammatory skin disease which comprising applying thereto a composition comprising 8-hydroxyquinoline in free form dissolved in a pharmaceutically acceptable essentially anhydrous solvent.

5 2. A method according to claim 1 wherein 8-hydroxyquinoline is present in the composition in an amount of from 0.01 to 5.0% by weight.

3. A method according to claim 2 wherein 8-hydroxyquinoline is present in an amount of from 0.1 to
10 1.0% by weight.

4. A method according to claim 1, 2 or 3 wherein the said solvent is oleophilic and water-immiscible.

5. A method according to claim 4 wherein the essentially anhydrous oleophilic, water-immiscible solvent
15 comprises a mixture of white soft paraffin and isopropyl myristate.

6. A method according to any one of claims 1 to 5 wherein the composition also comprises an antioxidant.

7. A method according to any one of the preceding
20 claims wherein the composition also comprises a topical corticosteroid.

8. A method according to claim 7 wherein the topical corticosteroid is betamethasone valerate present in an amount of from 0.01 to 1.0% by weight.

25 9. A method according to any one of claims 1 to 8 wherein the essentially anhydrous solution of 8-hydroxyquinoline is dispersed in an aqueous phase which has a substantially neutral pH.

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10. A method according to claim 9 wherein the said aqueous phase contains an anionic dispersing agent.

11. A method according to claim 9 or 10 wherein 0 to 0.2% by weight of phenoxyethanol is dissolved in the aqueous phase.

12. A method according to claim 1, 2 or 3 wherein the composition is in the form of a gel in which the 8-hydroxyquinoline in free form is dissolved in an essentially anhydrous pharmaceutically acceptable solvent gelled with a thickener.

13. A method according to claim 12 wherein the said solvent is ethanol and the said thickener is hydroxypropylcellulose.

14. A method according to any one of claims 1 to 13 for the treatment of psoriasis.

15. A method according to claim 1 substantially as hereinbefore described.

DATED THIS 21ST DAY OF OCTOBER 1996

DIOMED DEVELOPMENTS LIMITED
By its Patent Attorneys:
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Fellows Institute of Patent
Attorneys of Australia

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ABSTRACT

COMPOSITIONS FOR THE TREATMENT OF
INFLAMMATORY PROLIFERATIVE SKIN DISEASE AND THEIR USE

8-Hydroxyquinoline is useful in the topical treatment of inflammatory proliferative skin diseases, especially psoriasis. It should be applied from an essentially anhydrous vehicle.

