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Fortsættes ...



# DESCRIPTION

## FIELD OF THE INVENTION

**[0001]** The present invention concerns pharmaceutical compositions for dermal use which contain at least one vitamin D or vitamin D analogue and at least one corticosteroid. More specifically, the invention relates to pharmaceutical compositions containing two or more pharmacologically active compounds which have low compatibility with respect to the pH value of optimum stability, preferably, said pharmacologically active compounds are at least one vitamin D analogue and at least one corticosteroid.

## BACKGROUND OF THE INVENTION

**[0002]** In the treatment of a number of conditions using dermal application, e.g. in the treatment of psoriasis, it is often indicated to employ a combination treatment incorporating two or even more different pharmacologically active compounds. Thus, in the treatment of e.g. psoriasis, it is common to use a combination treatment involving a steroid compound, such as a corticosteroid compound, and a vitamin D analogue such as calcipotriol, and where each of the active compounds are formulated in separate preparations.

**[0003]** Until now (except for example 8 of WO94/14453) a topical pharmaceutical composition comprising a combination of a vitamin D analogue and a topical steroid has not been described. Moreover, these two types of compounds often have optimum stability values of pH that differ significantly from one another making it non-obvious to attempt to prepare a topical pharmaceutical preparation containing a steroid compound together with a vitamin D analogue. US patent No. 5,565,462 relates to topical pharmaceutical compositions containing certain xanthine compounds, and where said compositions may additionally contain active compounds, such as steroids and vitamin D and its derivatives. However, there is no disclosure of a topical composition containing both a steroid and a vitamin D or vitamin D analogue or derivative, nor is there any description of a method of preparing such a composition.

**[0004]** The following example describes the difficulties encountered when the skilled person wishes to prepare a combination composition for topical use comprising both a vitamin D or a vitamin D analogue or derivative and a topical steroid: The vitamin D analogue calcipotriol, as well as other examples of vitamin D analogues, requires a pH value above 8 for maximum stability, whereas corticosteroids such as Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) require pH values in the range of 4-6 for maximum stability. Since the base auxiliary materials and additives traditionally used in preparing topical formulations, such as creams and/or ointments, involve having some kind of acid or alkaline nature or reaction ability, it has therefore hitherto not been possible to combine the two active compounds in one single formulation while maintaining good stability of the active compounds

(see also Patel et al., 1998, J. Am. Acad. Dermatol. 38:1010-1, where compositions were mixed extemporaneously).

**[0005]** Consequently, physicians have had to resort to letting patients under this type of two-component regimen perform sequential application of two creams/ointments, each containing one of the compounds formulated at its maximum stability pH. This may lead to incompatibility of the preparations so that patients must, e.g., apply one cream/ ointment in the morning and the other in the evening. Needless to say, patient compliance as well as correct administration dosage is a problem under such circumstances. Richards, H.L. et al. report in J Am Acad Dermatol 1999 Oct; 41(4):581 -3 on a study of patients with psoriasis and their compliance with medication. They report that poor compliance with treatment advice in chronic conditions, such as psoriasis, represents a major challenge to health care professionals: Thirty-nine percent of participants reported that they did not comply with the treatment regimen recommended. The noncompliant group had a higher self-rated severity of psoriasis, were younger, and had a younger age at onset than those who were compliant. The noncompliant group reported that psoriasis had a greater impact on daily life.

**[0006]** It is therefore an object of the present invention to provide a pharmaceutical composition for dermal use where said composition alleviates the inconveniences of a two-component or multi-component regimen for the treatment of psoriasis and other inflammatory skin diseases including nail diseases. The provision of said composition will result in a substantial improvement in quality of life for a large population of psoriasis patients, especially the noncompliant group having a higher self-rated severity of psoriasis, being younger, and having a younger age at onset than those who are compliant.

#### **SUMMARY OF THE INVENTION**

**[0007]** In order to solve the above mentioned problems, the invention provides a pharmaceutical composition, in the form of a mono-phase ointment, for dermal use in the topical treatment of psoriasis, said composition comprising a first pharmacologically active component A consisting of calcipotriol or its hydrate, and a second pharmacologically active component B consisting of betamethasone or an ester thereof.

**[0008]** The invention also provides a topical pharmaceutical composition in the form of an ointment which is non-aqueous, said composition comprising a first pharmacologically active component A consisting of calcipotriol or its hydrate, and a second pharmacologically active component B consisting of betamethasone or the 17-valerate or 17,21-dipropionate ester thereof.

**[0009]** The invention also provides a pharmaceutical composition for dermal use in the form of an ointment, said composition comprising 52.2µg/g calcipotriol hydrate and 0.643mg/g betamethasone dipropionate.

**DETAILED DESCRIPTION OF THE INVENTION**

**[0010]** First pharmacologically active component A is calcipotriol.

**[0011]** Second pharmacologically active component B is Betamethasone (9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione) and esters thereof such as the 21-acetate, 17-adamantoate, 17-benzoate, 17-valerate, and 17,21-dipropionate. More preferred esters are the 17-valerate or the 17,21-dipropionate.

**[0012]** The pharmaceutical compositions can exhibit a higher efficacy in the treatment of psoriasis in humans and other mammals than any of the pharmacologically active components used alone. Said efficacy is preferably measured as percentage change in PASI score in psoriasis.

**[0013]** PASI (Psoriasis Area and Severity Index) score assesses the extent and severity of the patient's psoriasis. The following formulae are used to calculate the PASI score:

Arms	$0.2(R+T+S)E = X$
Trunk	$0.3(R+T+S)E = Y$
Legs	$0.4(R+T+S)E = Z$

where R=score for redness, T=score for thickness, S=score for scaliness, and E=score for extent where the score is assessed according to a scale from 0 to 4 as follows: 0=no involvement, 1=<10%, 2=10-29%, 3=30-49%, and 4=50-69%. The sum of X+Y+Z gives the total PASI score which can range from 0 to 64.8.

**DESCRIPTION OF THE DRAWINGS**

**[0014]**

Fig. 1 is a graphic illustration of the percentage change in PASI score obtained during 4 weeks of clinical trial where the efficacy of a preparation according to the invention containing calcipotriol hydrate (52.2µg/g) and betamethasone dipropionate (0.643mg/g) is compared to that of a preparation in the same vehicle containing only calcipotriol hydrate (52.2µg/g) and a preparation in the same vehicle of betamethasone dipropionate (0.643mg/g). Fig. 1 shows an efficacy of the preparation of the invention which by far exceeds the efficacy obtainable by the two single component preparations. The change in PASI score reflects in the group of patients treated with the preparation of the invention a success of treatment of psoriasis hitherto unattainable by treatment with commercial preparations containing either calcipotriol or betamethasone, or by alternating treatment with such commercial preparations thus proving the advantage of having the two active components present in the same preparation. (EOT=end of treatment).

Fig. 2 is a table showing the figures for percentage change in PASI score at each visit and end of treatment for the same clinical trial as described for Fig. 1.

Fig. 3 is a bar diagram showing percentage of responders as a result of investigators' assessment of overall efficacy at each visit and end of treatment in the same clinical trial as for Fig. 1. Responders are defined as patients with marked improvement or clearance

Fig. 4 is a table showing the figures for percentage of responders as a result of investigators' assessment of overall efficacy at each visit and end of treatment, cf. Fig. 3, in the same clinical trial as for Fig. 1.

### **TOPICAL FORMULATIONS**

**[0015]** The invention provides a topical pharmaceutical composition in the form of an ointment which is, preferably, non-aqueous. In one preferred embodiment, the composition of the invention is a mono-phase composition, i.e. a composition comprising a single solvent system, such as an ointment.

**[0016]** A non-aqueous pharmaceutical composition for dermal use can comprise

a first pharmacologically active component A consisting of calcipotriol;

a second pharmacologically active component B consisting of betamethasone or an ester thereof;

the difference between the optimum stability pH of a first pharmacologically active component A and the optimum stability pH of a second pharmacologically active component B being at least 1; and

at least one solvent component C selected from the group consisting of:

1. (i) compounds of the general formula  $R^3(OCH_2C(R^1)H)_xOR^2$  (I) wherein x is in the range of 2-60,  $R^1$  in each of the x units independently is H or  $CH_3$ ,  $R^2$  is straight chain or branched  $C_{1-20}$ alkyl or benzoyl, and  $R^3$  is H or phenylcarbonyloxy;
2. (ii) di-(straight or branched)- $C_{4-10}$  alkyl esters of  $C_4$ - $C_8$  dicarboxylic acids;
3. (iii) straight or branched  $C_{12-18}$ -alkyl benzoates;
4. (iv) straight or branched  $C_{2-4}$ -alkyl esters of straight or branched  $C_{10-18}$ -alkanoic or -alkenoic acids;
5. (v) propylenglycol diesters with  $C_8$ - $C_{14}$ -alkanoic acids; and
6. (vi) branched primary  $C_{18-24}$  alkanols, and

wherein components A and B are as defined above.

**[0017]** It has been found that in such combination compositions containing a solvent component C, the active components can co-exist without degradation, despite their different pH/stability profiles. The tendencies of the active compounds to affect one another with regard to pH is minimised or eliminated.

**[0018]** It is preferred that the maximum difference in optimum stability pH between the pharmacologically active compounds is at least 1.5, more preferred at least 2, in particular at least 2.5, more particularly at least 3, especially at least 4, such as at least 5.

**[0019]** In the general formula (I) defined above, it is preferred that the factor x (which designates the number of the units within the parentheses) is in the range 4-50, more preferably 4-40, in particular 4-30, especially 5-25, more especially 10-20, such as about 15. It is further preferred that R<sup>1</sup> is CH<sub>3</sub>.

**[0020]** It is preferred that said component C is selected from compounds of the general formula H(OCH<sub>2</sub>C(R<sup>1</sup>)H)<sub>x</sub>OR<sup>2</sup> (II) where R<sup>1</sup>, x, and R<sup>2</sup> are as defined above, and mixtures thereof.

**[0021]** As non-limiting specific examples of the types (i)-(vi) of the solvent component C defined above may be mentioned the following, including trade names:

Arlamol E (polyoxypropylene (15) stearyl ether);

Arlamol DoA (diisooctyl ester of adipic acid);

Arlasolve 200 (Polyoxyethylene-20-isohexadecyl ether);

Eutanol G (2-octyldodecanol);

Finsolv (Isostearyl benzoate);

Finsolv P (polyoxypropylene-15-stearyl ether benzoate);

Isopropylesters of straight or branched C<sub>10</sub> - C<sub>18</sub> alkanolic or alkenolic acids such as isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate and isopropyl monooleate;

Miglyol 840 (Propylene glycol diester of caprylic and caprinic acid);

DPPG (propylene glycol dipelargonate);

Procetyl AWS (CH<sub>3</sub>(CH<sub>2</sub>)<sub>14</sub>CH<sub>2</sub>(OCH(CH<sub>3</sub>)CH<sub>2</sub>)<sub>5</sub>-(OCH<sub>2</sub>)<sub>20</sub>OH).

**[0022]** The compositions of the present invention may be prepared in accordance with methods well known to the person skilled in the field of pharmacy. Thus, the non-aqueous compositions may be prepared by incorporating the components into a well known ointment or lotion base excipient such as white soft paraffin (also known as vaseline) or Plastibase™ (a base prepared from polyethylene (average MW about 21,000) and paraffin liquid) or ESMA-P™ (a microcrystalline wax). As an example, preparation of a composition according to the invention is typically performed by melting white soft paraffin, adding a solution (typically at a concentration in the range of 0.0005-2.5% w/w) of the vitamin D analog in the required amount of solvent component C, e.g. Arlamol E, followed by addition of a dispersion of the corticosteroid component B in paraffin oil, typically with a particle size of from 0.1 to 20 µm, and then cooling the mixture. Typical content ranges of the various components in the finished composition according to the invention are 0.005 to 0.1% w/w of the corticosteroid component B, from 0.0001 to 0.025% w/w of the vitamin D analog component A, and from 1 to 20% w/w of the solvent component C, the remainder typically being primarily base excipient such as the above-mentioned white soft paraffin and/or paraffin oil. The composition may also contain other commonly used additives such as antioxidants (e.g. α-tocopherol).

**[0023]** The composition according to the invention provides the following therapeutic advantages in the treatment of skin diseases, such as psoriasis, sebo-psoriasis and related disorders, compared to the single compound therapy or combination therapy of the prior art:

- A clinical investigation has showed that treatment of psoriasis patients with a composition according to the invention comprising calcipotriol and betamethasone resulted in a faster onset of healing and a more effective healing of plaques than patients treated with only one of the active compounds.
- A composition combining a vitamin D analogue and a topical steroid provides synergy in the form of additional benefit to the patient apart from the direct therapeutic value of the active substances. It has been shown that the skin irritative side effects of a vitamin D analogue, such as calcipotriol, is alleviated by the simultaneous application of a steroid, such as betamethasone, onto psoriatic skin, an effect that is only attainable using a two-component or multi-component treatment regimen where a vitamin D analogue and a steroid cannot be applied simultaneously to affected skin due to incompatibility of the preparations. When both a vitamin D analogue and a topical steroid are used in a combination treatment of psoriasis it has hitherto been necessary to use separate applications, typically one in the morning and the other in the evening, making it impossible to obtain any synergistic effect of the two types of active compounds (*cf.* Ortonne, J.P., *Nouv. Dermatol.*, 1994, 13(10), p. 746-751), or where a certain degree of synergistic effect, such as less skin irritation, has been reported for a two-component regiment (*cf.* Kragballe, K. et al. *Br J Dermatol* 1998 Oct;139(4):649-54, and Ruzicka, T. et Lorenz, B. *Br J Dermatol* 1998, 138(2), 254-58) a substantial proportion of psoriasis patients will not benefit due to non-compliance with the treatment regimen.
- Satisfactory medical treatment of skin disorders, such as psoriasis, can be attained in a shorter period of time using the composition according to the invention resulting in a reduction of steroid side effects, such as skin atrophy and rebound. Besides, it can be



anticipated that even a milder acting steroid of group I, such as hydrocortisone which is presently not administered for psoriasis treatment, will be efficient in reducing or even eliminating the skin irritation which often follows calcipotriol treatment.

- Thus, the tolerance of the treatment will be considerably improved due to reduction of side effects of the active compounds.
- Instructions for treatment will be simpler when a single preparation is needed resulting in improved compliance for the patient and the possibility of efficient treatment of a much larger population of psoriasis patients.
- Instructions for treatment will be simpler when a single preparation is needed resulting in improved safety for the patient.

**[0024]** Psoriasis and related skin diseases can be treated by topically administering an effective amount of a composition according to the invention to a patient in need of such treatment. Said method preferably comprises topical administration once or twice daily of a medically sufficient dosage of said composition.

**[0025]** The composition according to the invention preferably contains 0.001-0.5 mg/g or ml or more preferably 0.001-0.25 mg/g or ml of said component A and 0.05-0.1 mg/g or ml of said component B.

**[0026]** The invention is further illustrated by the following, non-limiting examples.

#### **EXAMPLE 1**

##### ***Ointment containing Calcipotriol and Betamethasone dipropionate***

**[0027]** 919,3 g of White Soft Paraffin is melted at 80°C followed by cooling to 70°C and maintaining that temperature. Thereafter, 52.2 mg Calcipotriol hydrate (50 mg Calcipotriol) is dissolved in 50 g Arlamol E (polyoxypropylene-15-stearyl ether) to form a solution (Solution 1). Solution 1 is then added slowly into the molten paraffin while stirring.

**[0028]** Betamethasone (0,5 g, in the form of 0.643g of its dipropionate) in particulate form (99% <15µm) is dispersed in 30 g Paraffin Liquid to form Dispersion 1. Dispersion 1 as well as 20 mg α-tocopherol are added to the Calcipotriol-containing paraffin mixture of while stirring, after which the mixture is cooled to below 30°C to give a composition according to the invention with the following composition:

1 g of ointment contains:	Betamethasone (as dipropionate 0.643 mg)	0.5mg
	Calcipotriol (as hydrate 52.2 µg)	50 µg

	Paraffin, Liquid	30 mg
	Polyoxypropylene-15-Stearyl Ether	50 mg
	$\alpha$ -Tocopherol	20 $\mu$ g
	White Soft Paraffin	to make 1 g

**EXAMPLE 2****Stability test**

[0029] The chemical stability of the two active components was tested after storage for 1 month at 40°C and 3 months at 25°C and 40°C, respectively. The quantitative content of Calcipotriol was determined by HPLC.

[0030] The Calcipotriol was extracted from the preparation into a mixture of methanol and 0.01M diammonium hydrogenphosphate (70:30) and quantified under the following HPLC conditions: Column: about 125 mm Ø 4 mm (i.d.) stainless steel column with LiChrospher RP-18, 5  $\mu$ m; mobile phase: acetonitrile-methanol-0.01 M aqueous ammonium phosphate pH 6 (20:50:30); flow: about 2 ml/min; detection: variable wavelength UV-detector set at 265 nm. Calcipotriol and the related substances were separated by the reverse phase HPLC-method described above; Column: Superspher RP-18, 4  $\mu$ m; Flow: 1.2 ml/min. The quantitative content of Betamethasone Dipropionate was determined by HPLC.

[0031] The Betamethasone Dipropionate was extracted from the preparation into a mixture of acetonitrile:water (50 : 55) and quantified under the following HPLC conditions: Column: About 125 mm Ø 4 mm (i.d.) stainless steel column packed with LiChrospher RP-18, 5 $\mu$ m. Mobile phase: Acetonitrile: water (50 : 55). Flow: 2 ml/min. Detection: Variable wavelength UV-detector set at 240 nm. The related substances besides betamethasone were determined by a reverse phase HPLC-method analogous to the above. Betamethasone: Determined as above with the exception of the mobile phase: Acetonitrile/methanol/0.05M buffer pH7 (25:5:70).

[0032] The results are shown in the following Table 1.

Table 1

	Calcipotriol $\mu$ g/g	Calcipotriol related substances %	Betamethasone dipropionate Mg/g	Betamethasone related substances %
Start	50.0	1.6	0.63	1.2
25°C				

	Calcipotriol µg/g	Calcipotriol related substances %	Betamethasone dipropionate Mg/g	Betamethasone related substances %
3 months	50.5	1.4	0.64	0.2
<u>40°C</u>				
1 month	48.0	2.1	0.64	0.6
3 months	49.7	1.8	0.64	0.2

**[0033]** It will be seen from Table 1 that both Calcipotriol and Betamethasone ester are very stable under the test conditions.

**[0034]** The stability of Calcipotriol was compared to a similar ointment where propylene glycol was used as the solvent and lanolin used as an emulsifier. The composition of the comparison ointment was the same as the above with respect to Calcipotriol and Betamethasone dipropionate, as well as 10% w/w propylene glycol, 10% w/w anhydrous lanolin and 80% w/w White Soft Paraffin. The comparison ointment was stored for 2.5 months at 5°C and 40°C, respectively. Only the content of Calcipotriol-related substances was determined in the manner described above. The results are shown in Table 2.

Table 2

Calcipotriol related substances %	
5°C	20
40°C	96

**[0035]** As it will be seen from the results, Calcipotriol is degraded almost completely in the comparison composition under the test conditions as opposed to a composition of the invention, where the Calcipotriol is retained with essentially no degradation.

### **EXAMPLE 3 (for reference)**

#### **Medical skin lotion comprising a two phase solvent system**

**1 g contains**

[0036]

Betamethasone (As Dipropionate 0,643 mg)	0.5 mg
Calcipotriol (as Hydrate 52.2 µg)	50 µg
Disodium Phosphate Dihydrate	2.5 mg
Diazolidinyl Urea	3 mg
Polyoxypropylene-15-Stearyl Ether (Arlamol® E)	50 mg
Isohexadecan (Arlamol® HD)	200 mg
Polyoxyethylene-2-Stearyl Ether (Brij® 72)	30 mg
Water, purified	to make 1 g

**Procedure for the preparation of 1 kg of lotion:**

**[0037]** 2.5 g Disodium Phosphate and 3.9 Diazolidinyl Urea are dissolved in about 714 g water. The solution is heated to 60 -70°C to obtain the water phase. 30 g Polyoxyethylene-2-Stearyl Ether is melted together with 200 g Isohexadecan at 60-70°C and a solution of 52.2 mg Calcipotriol Hydrate in 50 g Polyoxypropylene-15-Stearyl Ether is added to obtain the oil phase. The two phases are mixed during homogenisation, 643 mg Betamethasone Dipropionate is dispersed into the mixture, and the lotion is cooled during mixing to room temperature. The preparation is stable at 25°C for > 14 days.

**REFERENCES CITED IN THE DESCRIPTION**

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**Patentkrav**

1. Farmaceutisk sammensætning, i form af en mono-fase-salve, til dermal  
anvendelse i den topiske behandling af psoriasis, hvilken sammensætning  
omfatter en første farmakologisk aktiv komponent A bestående af calcipotriol eller  
5 dets hydrat, og en anden farmakologisk aktiv komponent B bestående af  
betamethason eller en ester deraf, såsom 17-valerat- eller 17,21-  
dipropionatester.
2. Sammensætning til anvendelse ifølge krav 1, hvor komponent B er  
10 betamethason-17,21-dipropionat.
3. Sammensætning til anvendelse ifølge et hvilket som helst af de foregående  
krav, omfattende mindst én farmaceutisk acceptabel bærer, opløsningsmiddel  
eller fortyndingsmiddel.  
15
4. Sammensætning til anvendelse ifølge krav 3, omfattende mindst ét  
farmaceutisk acceptabelt opløsningsmiddel.
5. Sammensætning til anvendelse ifølge et hvilket som helst af de foregående  
20 krav, hvor sammensætningen omfatter calcipotriolhydrat i en mængde på 52,2  
µg/g og betamethasondipropionat i en mængde på 0,643 mg/g.
6. Sammensætning til anvendelse ifølge et hvilket som helst af de foregående  
krav, hvor sammensætningen administreres én eller to gange dagligt i en  
25 medicinsk tilstrækkelig dosis.
7. Sammensætning til anvendelse ifølge et hvilket som helst af de foregående  
krav, hvor sammensætningen er ikke-vandig.
- 30 8. Topisk farmaceutisk sammensætning i form af en salve der er ikke-vandig,  
hvilken sammensætning omfatter en første farmakologisk aktiv komponent A  
bestående af calcipotriol eller dets hydrat, og en anden farmakologisk aktiv

komponent B bestående af betamethason eller 17-valerat- eller 17,21-dipropionatester deraf.

- 5 **9.** Fremgangsmåde til fremstilling af en ikke-vandig sammensætning ifølge et hvilket som helst af kravene 7 eller 8, omfattende inkorporering af komponent A og komponent B ind i en salvebasisexcipiens; fx, hvor salvebasisexcipiensen er: hvid blød paraffin; en basis fremstillet fra polyethylen (gennemsnitlig molekylvægt omkring 21.000) og paraffinvæske; eller en mikrokrySTALLINSK voks.
- 10 **10.** Fremgangsmåde til fremstilling af en ikke-vandig sammensætning ifølge et hvilket som helst af kravene 7 eller 8, omfattende: at smelte hvid blød paraffin, tilsætte en opløsning af komponent A i den krævede mængde opløsningsmiddel, efterfulgt af tilsætning af en dispersion af komponent B i paraffinolie, og derefter afkøle blandingen.
- 15 **11.** Farmaceutisk sammensætning til dermal anvendelse i form af en salve, hvilken sammensætning omfatter 52,2 µg/g calcipotriolhydrat og 0,643 mg/g betamethasondipropionat.

## DRAWINGS

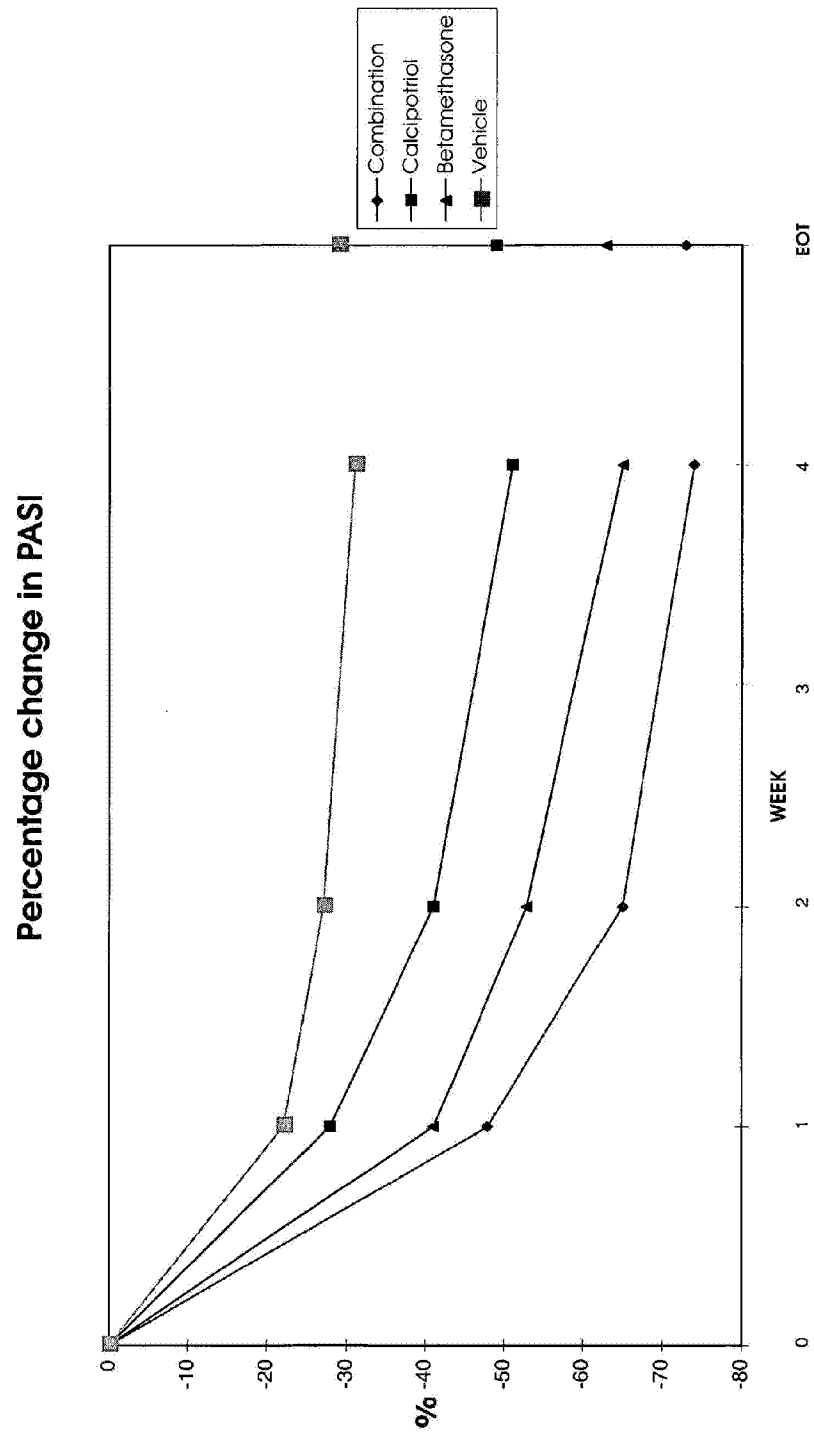


FIGURE 1



**Percentage change in PASI score at each visit and  
end of treatment**

Percentage change in PASI score	COMB (n=301)	CALC (n=308)	BETA (n=312)	VEHICLE (n=107)
<b>Visit 1</b>				
Mean	10.9	10.9	10.7	10.6
<b>Percentage change</b>				
<b>To visit 2</b>				
Mean	-48.1	-28.4	-41.4	-21.5
<b>To visit 3</b>				
Mean	-64.9	-40.8	-53.2	-27.4
<b>To visit 4</b>				
Mean	-73.9	-51.3	-64.5	-31.3
<b>To end of treatment</b>				
Mean	-73.2	-48.8	-63.1	-28.8

**FIGURE 2**

Responders (Investigator's assessment)

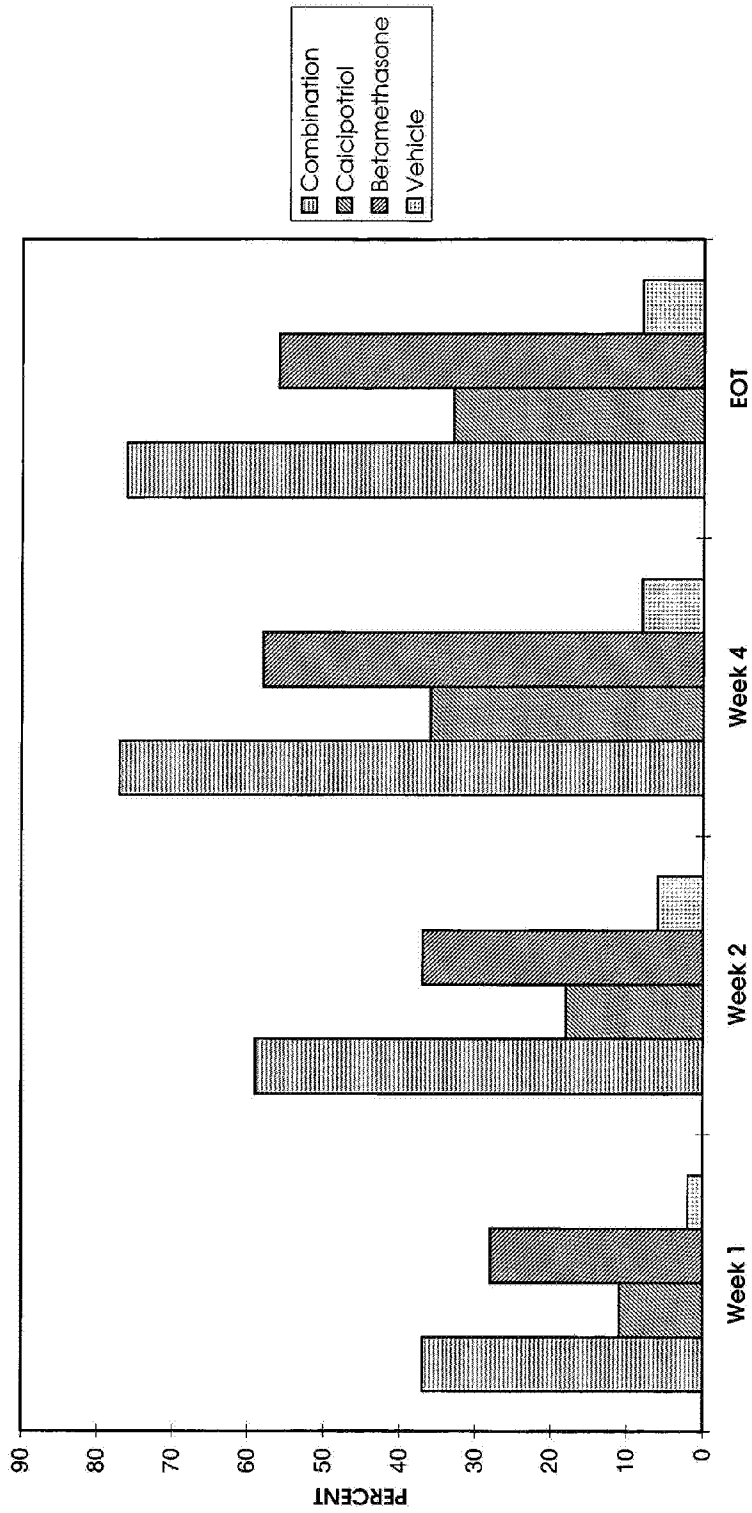


FIGURE 3

### Investigator's assessment of overall Efficacy at each visit and end of treatment

Investigator's overall efficacy assessment	COMB (n=301) %	CALC (n=308) %	BETA (n=312) %	VEHICLE (n=107) %
<b>Visit 2</b>				
Non responder	63.5	89.5	72.5	98.1
Responder	36.5	10.5	27.5	1.9
Total	100.0	100.0	100.0	100.0
<b>Visit 3</b>				
Non responder	41.5	82.2	62.7	94.2
Responder	58.5	17.8	37.3	5.8
Total	100.0	100.0	100.0	100.0
<b>Visit 4</b>				
Non responder	23.1	64.4	42.4	91.9
Responder	76.9	35.6	57.6	8.1
Total	100.0	100.0	100.0	100.0
<b>End of treatment</b>				
Non responder	23.9	66.6	44.2	92.5
Responder	76.1	33.4	55.8	7.5
Total	100.0	100.0	100.0	100.0

**FIGURE 4**