1 578 072

PATENT SPECIFICATION (11) 1 578 072

(21) Application No. 6042/77 (22) Filed 14 Feb. 1977
(31) Convention Application No. 660963
(32) Filed 24 Feb. 1976 in
(33) United States of America (US)
(44) Complete Specification published 29 Oct. 1980
(51) INT CL³ A61K 31/57 (A61K 31/57 31/23)
(52) Index at acceptance
A5B 170 190 211 216 21Y 244 24X 24Y 26Y 327 381 38Y 390 39X J

(19)

(54) TOPICAL STEROID FORMULATIONS

(71) We, E. R. SQUIBB & SONS, INC., a corporation organised under the laws of the State of Delaware, United States of America, of Lawrenceville-Princeton Road, Princeton, New Jersey 08540, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to topical steroid formulations which include one or more ricinoleates, such as castor oil, as a vehicle for the steroid. The term "ricinoleates" as employed throughout this specification and in the claims excludes salts of ricinoleic acid.

Topical steroid formulations containing 21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17-acetonide as the active ingredient are extensively employed in the treatment of skin disorders, such as dermatitis. To be therapeutically effective, the active ingredient must be in a molecular dispersion to facilitate desired percutaneous absorption which is particularly important in achieving a therapeutic response for the management of psoriasis. Unfortunately, the above steroid is insoluble in water (less than 0.0005% soluble) and is even less soluble in hydrocarbon vehicles such as mineral oil, petrolatum or polyethylene gelled mineral oil. Various organic solvents and solubilizers have been found to be good solvents for such steroid. However, they have been found to be unsuitable for commercial application for reasons such as their high volatility and low boiling points, their disagreeable odor, their "paint removing" property, and their undesirable skin reaction. Furthermore, various water-soluble emulsifiers and oil liquids or emmolients have been suggested for use in preparing creams or lotions. However, because of the undesirably low solubility of the steroid in such vehicles, higher levels of these materials in topical products are required thereby increasing their cost and also adversely affecting their cosmetic elegance.

Accordingly, in view of the above considerations, it is seen that a need exists for a suitable vehicle capable of solubilizing a sufficient amount of the steroid so that it may be employed in a topical formulation, while being dermatologically beneficial, stable, and pharmaceutically acceptable.

According to the present invention there is provided a composition for topical application in the form of a cream or lotion, comprising at least one steroid selected from 21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,;17α - triol - 3,20 - dione 16,17-acetonide; 21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b] - [1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1); and 9α - fluoro - 11β,16α,17,21 - tetrahydroxy - pregna - 1,4 - diene - 3,20 - dione 16,17-acetonide, a ricinoleate vehicle (as hereinbefore defined) in which said steroid is at least partially soluble, polyethylene glycol fatty alcohol ether as an emulsifier-thickener, an oleaginous material or emollient, a preservative and water.

The ricinoleate vehicle may comprise one or more ricinoleates alone or in admixture with fatty acids or other vehicles and may be present in amounts within the range of from about 0.5 to about 20% by weight and preferably from about 1 to about 15% by weight of the steroid formulation depending upon the particular steroid employed. The preferred ricinoleate vehicle suitable for use herein is castor oil, that is ricinus oil or triglyceride of fatty acids, the fatty acid composition being approximately 87% glyceryl ricinoleate, 7% oleic acid, 3% linoleate, 2% palmitate,

1% stearate and trace amounts of other compounds such as dihydroxystearic acid. Other examples of suitable ricinoleate vehicles include, but are not limited to, propylene glycol monoricinoleate, diglycol ricinoleate, and water-insoluble polyethylene glycol ricinoleates. It is to be understood that the oleaginous material present in the composition of the present invention is in addition to the ricinoleate vehicle.

The steroid is preferably present in an amount of from about 0.005 to about 0.6% by weight, and more preferably from about 0.025 to about 0.2% based on the total weight of the composition, depending upon the type of steroid employed and its solubility in the ricinoleate vehicle. As will be seen hereinafter, other active ingredients may be employed in conjunction with the steroid. In such case, the other active ingredients, such as econazole, nystatin, neomycins and gramicidins, or mixtures thereof, may be employed, preferably in amounts up to 2%.

The topical steroid formulations of the invention may take the form of a lotion or cream, that is, those formulations which include a relatively large aqueous phase and a relatively small oil phase. Furthermore, the lotions and creams of the invention may include the steroid component "all-in-solution" in the oil phase so that substantially no steroid crystallizes out at room temperature. Alternatively, the lotion or cream may comprise a biphasic system, that is, a system wherein a portion (from about 30 to about 75% by weight) of the steroid is in solution in the oil phase and the remainder of the steroid is in suspension in the aqueous phase.

With regard to the cream formulations of the invention where the steroid is to be all-in-solution, the cream will preferably contain from about 0.005 to about 0.6% and more preferably from about 0.025 to about 0.2% by weight of the active ingredient based on the weight of the entire cream formulation, and from about 0.5 to about 16% and preferably from about 1 to about 14% by weight of the ricinoleate vehicle based on the weight of the entire cream formulation and depending upon the solubility of the particular steroid in the particular ricinoleate employed. The all-in-solution cream formulation will preferably also include in the oil phase, in addition to the steroid and ricinoleate vehicle, from about 5 to about 14% and more preferably from about 8 to about 12% by weight of the emulsifier-thickener based on the weight of the entire cream formulation, and from about 2 to about 8% and preferably from about 3 to about 5% by weight of oleaginous material or emollient based on the weight of the entire cream formulation. The oil phase may also optionally include an anti-whitening agent or anti-foaming agent in an amount within the range of from about 0.2 to about 3% and preferably from about 0.5 to about 1.5% by weight based on the entire cream formulation. An antioxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.04% and preferably from about 0.01 to about 0.03% by weight based on the entire cream formulation.

The aqueous phase of the all-in-solution cream formulation will preferably contain a glycol-type preservative such as propylene glycol in an amount within the range of from about 10 to about 50% and more preferably from about 12 to about 40% by weight of the entire cream formulation and/or a paraben or other conventional type preservative such as methyl and/or propyl paraben in an amount ranging from about 0.05 to about 0.5%, and purified water in an amount within the range of from about 30 to about 70% by weight and preferably from about 35 to about 65% by weight of the entire cream formulation.

With regard to the cream formulation of the invention in the form of the biphasic system, the cream will preferably contain from about 0.005 to about 0.6% and more preferably from about 0.025 to about 0.2% by weight of the active ingredient based on the weight of the entire cream formulation, and from about 0.5 to about 14% and preferably from about 1 to about 8% by weight of the ricinoleate vehicle based on the weight of the entire cream formulation, depending upon the solubility of the particular steroid in the particular ricinoleate vehicle employed. The biphasic cream formulation will preferably also include in the oil phase, in addition to the steroid and ricinoleate vehicle, from about 8 to about 12%, and more preferably from about 9 to about 11% by weight of the emulsifier-thickener based on the weight of the entire cream formulation, and from about 2 to about 8% and preferably from about 3 to about 6% by weight of oleaginous material or emollient based on the weight of the entire cream formulation. The oil phase may also optionally include an anti-whitening agent or anti-foaming agent in an amount within the range of from about 0.2 to about 3% and preferably from about 0.5 to about 1.5% by weight based on the entire cream formulation. An antioxidant may also optionally be included in an

amount within the range of from about 0.005 to about 0.04% and preferably from about 0.01 to about 0.03% by weight based on the entire cream formulation.

The aqueous phase of the biphasic cream formulation will preferably contain a preservative in an amount within the range of from about 10 to about 50% and more preferably from about 12 to about 40% by weight of the entire cream formulation, and purified water in an amount within the range of from about 30 to about 70% by weight and preferably from about 35 to about 65% by weight of the entire cream formulation.

With regard to the lotion formulation of the invention where the steroid is to be all-in-solution, the lotion will preferably contain from about 0.005 to about 0.6% and more preferably from about 0.025 to about 0.2% by weight of the active ingredient based on the weight of entire lotion formulation, and from about 0.5 to about 16% and preferably from about 1 to about 14% by weight of the ricinoleate vehicle based on the weight of the entire lotion formulation, depending upon the solubility of the particular steroid in the particular ricinoleate vehicle employed. The all-in-solution lotion formulation will preferably also include in the oil phase, in addition to the steroid and ricinoleate vehicle, from about 5 to about 14% and more preferably from about 8 to about 12% by weight of the emulsifier-thickener based on the weight of the entire lotion formulation, and from about 0.5 to about 6% and preferably from about 1 to about 5% by weight of oleaginous material or emollient based on the weight of the entire lotion formulation. The oil phase may also optionally include an anti-whitening agent or anti-foaming agent in an amount within the range of from about 0.2 to about 3% and preferably from about 0.5 to about 1.5% by weight based on the entire lotion formulation. An antioxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.04% and preferably from about 0.01 to about 0.03% by weight based on the entire lotion formulation.

The aqueous phase of the all-in-solution lotion formulation will preferably contain a glycol-type preservative in an amount within the range of from about 10 to about 50% and more preferably from about 12 to about 40% by weight of the entire lotion formulation, and/or a paraben or other conventional type preservative in an amount ranging from about 0.05 to about 0.5%, and purified water in an amount within the range of from about 50 to about 84% by weight and more preferably from about 60 to about 84% by weight of the entire lotion formulation.

With regard to the biphasic lotion formulation of the invention, the lotion will preferably contain from about 0.005 to about 0.6% and more preferably from about 0.025 to about 0.2% by weight of the active ingredient based on the weight of the entire lotion formulation, and from about 0.5 to about 14% and preferably from about 1 to about 8% by weight of the ricinoleate vehicle based on the weight of the entire lotion formulation, depending upon the solubility of the particular steroid in the particular ricinoleate vehicle employed. The biphasic lotion formulation will preferably also include in the oil phase, in addition to the steroid and ricinoleate vehicle, from about 1 to about 5% and more preferably from about 2 to about 4% by weight of the emulsifier-thickener based on the weight of the entire lotion formulation, and from about 0.2 to about 5% and more preferably from about 0.5 to about 4% by weight of oleaginous material or emollient based on the weight of the entire lotion formulation. The oil phase may also optionally include an anti-whitening agent or anti-foaming agent in an amount within the range of from about 0.2 to about 3% and preferably from about 0.5 to about 1.5% by weight based on the entire lotion formulation. An antioxidant may also optionally be included in an amount within the range of from about 0.005 to about 0.04% and preferably from about 0.01 to about 0.03% by weight based on the entire lotion formulation.

The aqueous phase of the biphasic lotion formulation will preferably contain a glycol-type preservative such as propylene glycol in an amount within the range of from about 8 to about 50% and more preferably from about 10 to about 40% by weight of the entire lotion formulation, and/or paraben-type or other preservatives at their recommended amount as described above, and purified water in an amount within the range of from about 50 to about 90% by weight and more preferably from about 60 to about 85% by weight of the entire lotion formulation.

With regard to specific steroid formulations, where 21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17-acetonide is employed in all-insolution creams or lotions, the ricinoleate vehicle will be preferably employed in an amount within the range of from about 3 to about 16% by weight and more preferably within the range of from about 5 to about 12% by weight depending upon the amount of steroid employed; in the case of biphasic formulations

containing the above steroid, the ricinoleate vehicle will be preferably employed in an amount within the range of from about 3 to about 14% by weight and more preferably from about 5 to about 10% by weight depending upon the amount of steroid employed.

Where 21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1) acetonide is employed in all-in-solution creams or lotions, the ricinoleate vehicle will be preferably employed in an amount within the range of from about 0.5 to about 5% by weight and more preferably within the range of from about 1 to about 4% by weight depending upon the amount of steroid employed; in the case of biphasic formulation containing the above steroid, the ricinoleate vehicle will be preferably employed in an amount within the range of from about 0.5 to about 4% by weight and more preferably from about 1 to about 3% by weight depending upon the amount of steroid employed.

Where 9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17-acetonide is employed in all-in-solution creams or lotions, the ricinoleate vehicle will be preferably employed in an amount within the range of from about 3 to about 16% by weight and more preferably within the range of from about 5 to about 12% by weight depending upon the amount of steroid employed; in the case of biphasic formulations containing the above steroid, the ricinoleate vehicle will be preferably employed in an amount within the range of from about 3 to about 14% by weight and more preferably from about 5 to about 10% by weight depending upon the amount of steroid employed.

The emulsifier-thickener suitable for use herein comprises ethers of polyethylene glycol and fatty alcohols, such as, Promulgen, Robinson Wagner Co., which contains some unreacted cetyl and stearyl alcohol, and other non-ionic emulsifying waxes such as Polawax, Croda Co.

The same emulsifier-thickener used in the cream formulation containing castor oil may also be obtained by substituting the above-mentioned emulsifying waxes with a mixture of polyoxyethylene (20) stearyl alcohol ether (BRIJ* 78, ICI) or Polyoxyethylene (20) cetyl alcohol ether (BRIJ 58, ICI) with cetyl or stearyl alcohol. The ratio of the BRIJ or a mixture of the two BRIJ with the fatty alcohol or a mixture of the two alcohols should be within the range of from about 0.6 to about 3.5, preferably from about 1 to about 3.

For 0.1% 21 - chloro - 9α - fluoro - Δ⁴ - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17-acetonide cream Promulgen type emulsifier-thickeners are preferred.

Emollients or oleaginous materials which may be incorporated in the formulations of this invention include petrolatum, glyceryl monooleate, myristyl alcohol and isopropyl palmitate.

The anti-foaming anti-whitening agent increases the elegancy of the cream or lotion and inhibits the formation of a white soapy look upon rubbing the cream or lotion on the skin. An example of such a material suitable for use herein is silicone fluid.

The cream or lotion may also contain an antioxidant such as butylated hydroxytoluene and butylated hydroxyanisole for retarding rancidity of the castor oil or other ricinoleate vehicle and for protecting the steroid against oxidation.

The preservative suitable for use herein may comprise propylene glycol or parabens (para-hydroxy benzoates) with the propylene glycol being preferred because of less incidence of skin sensitivity.

The following examples illustrate preferred embodiments of the present invention without, however, limiting the same thereto. All temperatures are expressed in degrees Centigrade.

Example 1

Lotion, 0.025% (all-in-solution)

21 - chloro - 9α - fluoro - Δ⁴ - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17 - acetonide, Micronized	0.025 gm.
Castor Oil, U.S.P.	5.0 gm.
Petrolatum, U.S.P.	1.2 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	3.0 gm.
Butylated Hydroxytoluene (BHT)	0.020 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

*BRIJ is a Registered Trade Mark.

The steroid and BHT are dissolved in castor oil with gentle heat not over 90°C. The petrolatum and Promulgen are melted together and heated to 75—80°C and then mixed with the steroid-BHT solution. The resulting mixture is added to a hot 75—80°C mixture of propylene glycol in 75 cc of purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48°C. Sufficient hot (48—50°C) purified water is then added to make 100 gm. Mixing is then continued at a slow rate during the congealing stage until the temperature of the lotion reaches 42°C.

Example 2

Lotion, 0.025% (biphasic)

21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17 - acetonide, Micronized	0.025 gm.
Castor Oil, U.S.P.	3.0 gm.
Petrolatum, U.S.P.	1.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	3.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

0.0125 gm of the steroid and BHT are dissolved in castor oil with gentle heat not over 90°C. Petrolatum and Promulgen D are melted together, heated to 75—80°C and mixed with the steroid-BHT mixture. The resulting mixture is added to a hot 75—80°C mixture of 10 gm propylene glycol in 75 cc of purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48°C and sufficient hot (48—50°C) purified water is added to make 94 gm. Agitation is continued at a slow rate until the temperature reaches 45°C and a congealed cream forms. The remainder of the steroid is dispersed homogeneously in 5 gm of propylene glycol. 10 gm of the congealed cream is added to the steroid-glycol mix with thorough mixing until homogeneous. The remainder of the congealed cream is then added as well as sufficient water to make 100 gm and the mixture is mixed for about half an hour until a homogeneous lotion is formed.

Example 3

Topical Cream, 0.1% (all-in-solution)

21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17 - acetonide, Micronized	0.1 gm.
Castor Oil, U.S.P.	12.5 gm.
Petrolatum, U.S.P.	4.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol Monostearate	0.3 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid, propylene glycol monostearate and BHT are dissolved in castor oil with gentle heat, not over 90°C. Petrolatum and Promulgen D are melted together, and silicone fluid is added. After mixing, the mixture is added to the castor oil solution with thorough mixing, maintaining the temperature at 75—80°C. Propylene glycol is mixed in 59 cc of water and heated to 80°C to form the aqueous phase which is added with vigorous agitation to the oil phase to emulsify. Agitation is continued until the temperature drops down to 48°C. Sufficient 50°C water is added to make 100 gm. Mixing is continued at a slow rate to congeal the mixture, until the temperature drops down to 42°C.

Example 4

Topical Cream, 0.1% (biphasic)

21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17 - acetonide, Micronized	0.1 gm.
Castor Oil, U.S.P.	5.0 gm.
Promulgen, Type D (PEG fatty alcohol ether)	10.0 gm.
Propylene Glycol Monostearate	0.3 gm.

Example 4

Topical Cream, 0.1% (biphase)

Petrolatum, U.S.P.	5.0 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol	15.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Purified Water, sufficient to make	100.0 gm.

0.05 gm of the steroid is dissolved in castor oil with gentle heat not over 90°C. BHT and propylene glycol monostearate are added and the mixture is heated to dissolve all solids. Petrolatum and Promulgen D are melted, mixed together and heated to 75—80°C. The two oil liquids are then mixed together with silicone oil and the temperature of the mixture is maintained.

10 gm. of propylene glycol and 60 cc of purified water are mixed together and heated to 75—80°C. The aqueous solution is then poured into the oil phase with vigorous agitation to emulsify.

Agitation is continued until the temperature drops down to 48°C. Sufficient water is added to the emulsion to weigh 94.5 gm. Agitation is continued at a slow rate for congealing. Stirring is stopped when temperature reaches 42°C. 0.5 gm of steroid is homogeneously dispersed in 5 gm of propylene glycol and 20 gm of the cream is added and mixed thoroughly. The remainder of the cream is added and mixed until homogeneous (for about half an hour) to form the cream of the invention.

Example 5

Topical Cream

21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17 - acetonide, Micronized (all-in-solution)	0.025 gm.
Econazole Nitrate	1.0 gm.
Castor Oil, U.S.P.	3.0 gm.
Petrolatum, U.S.P.	8.0 gm.
Promulgen, Type D	14.0 gm.
Silicone DC 200 Fluid	1.0 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid is dissolved in castor oil with gentle heat not over 90°C. Petrolatum and Promulgen D are melted, mixed with silicone oil and heated to 80—85°C and then mixed in the castor oil solution.

10 gm. of propylene glycol is dissolved in 57 cc. of purified water and heated to 80—85°C. The hot aqueous solution is added to the oil phase with vigorous agitation to emulsify. The mixture is cooled to 55°C, and sufficient water is added to make 94 gm. The mixture is mixed at a slow rate until the temperature drops to 42°C. The econazole nitrate is homogeneously dispersed in 5 gm of propylene glycol and the resulting dispersion is incorporated into the above cream and mixed well.

Example 6

Topical Cream

21 - chloro - 9α - fluoro - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17 - acetonide, Micronized (all-in-solution)	0.1 gm.
Castor Oil, U.S.P.	12.5 gm.
Nystatin	2.0 gm.
Petrolatum, U.S.P.	4.0 gm.
Promulgen, Type D (PEG fatty alcohol ether)	10.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid is dissolved in castor oil with gentle heat not over 90°C, and BHT is added with mixing to dissolve. Petrolatum and Promulgen D are melted and

heated to 80—85°C, silicone oil added thereto, and the mixture is incorporated into the castor oil portion. 10 gm. of propylene glycol is dissolved in 55 cc of water and heated to 80—85°C and poured into the oil phase with vigorous agitation to emulsify. Mixing is continued until the temperature drops down to 48°C. Sufficient water is added to make 93 gm and mixing is continued at a slow rate until the temperature of the congealed cream drops down to 42°C. Nystatin is dispersed in 5 gm of propylene glycol and incorporated into the cream by thorough mixing for about 20—30 minutes.

Example 7

Lotion, 0.025% (all-in-solution)

21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1)	0.025 gm.
Castor Oil, U.S.P.	1.5 gm.
Petrolatum, U.S.P.	1.2 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	3.0 gm.
Butylated Hydroxytoluene (BHT)	0.020 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid and BHT are dissolved in castor oil with gentle heat not over 90°C. The petrolatum and Promulgen are melted together and heated to 75—80°C and then mixed with the steroid-BHT solution. The resulting mixture is added to a hot 75—80°C mixture of propylene glycol in 75 cc of purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48°C. Sufficient hot (48—50°C) purified water is then added to make 100 gm. Mixing is then continued at a slow rate until the temperature of the cream reaches 42°C.

Example 8

Lotion, 0.025% (biphasic)

21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1)	0.025 gm.
Castor Oil, U.S.P.	1.0 gm.
Petrolatum, U.S.P.	1.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	3.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

0.0125 gm of the steroid and BHT are dissolved in castor oil with gentle heat not over 90°C. Petrolatum and Promulgen D are melted together, heated to 75—80°C and mixed with the steroid-BHT mixture. The resulting mixture is added to a hot 75—80°C mixture of 10 gm propylene glycol in 75 cc of purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48°C and sufficient hot (48—50°C) purified water is added to make 94 gm. Agitation is continued at a slow rate until the temperature reaches 45°C and a congealed cream forms. The remainder of the steroid is dispersed homogeneously in 5 gm of propylene glycol. 10 gm of the congealed cream is added to the steroid-glycol mix with thorough mixing until homogeneous. The remainder of the congealed cream is then added as well as sufficient water to make 100 gm and the mixture is mixed for about half an hour until a homogeneous lotion is formed.

Example 9

Topical Cream, 0.1% (all-in-solution)

21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1)	0.1 gm.
Castor Oil, U.S.P.	4.0 gm.
Petrolatum, U.S.P.	4.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.

Example 9

Topical Cream, 0.1% (all-in-solution)

Butylated Hydroxytoluene	0.02 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol Monostearate	0.3 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid, propylene glycol monostearate and BHT are dissolved in castor oil with gentle heat, not over 90°C. Petrolatum and Promulgen D are melted together, and silicone fluid is added. After mixing, the mixture is added to the castor oil solution with thorough mixing, maintaining the temperature at 75—80°C. Propylene glycol is mixed in 59 cc of water and heated to 80°C to form the aqueous phase which is added with vigorous agitation to the oil phase to emulsify. Agitation is continued until the temperature drops down to 48°C. Sufficient 50°C water is added to make 100 gm. Mixing is continued at a slow rate to congeal the mixture, until the temperature drops down to 42°C.

Example 10

Topical Cream, 0.1% (biphasic)

21 - chloro - 9 - fluoro - 2',3' - dihydro - 11 - hydroxy - 5' - phenylpregna - 1,4 - dieno[16,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1)	0.1 gm.
Castor Oil, U.S.P.	1.5 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.
Propylene Glycol Monostearate	0.3 gm.
Petrolatum, U.S.P.	5.0 gm.
Silicon Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol	15.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Purified Water, sufficient to make	100.0 gm.

0.05 gm of the steroid is dissolved in castor oil with gentle heat not over 90°C. BHT and propylene glycol monostearate are added and the mixture is heated to dissolve all solids. Petrolatum and Promulgen D are melted, mixed together and heated to 75—80°C. The two oil liquids are then mixed together with silicone oil and the temperature of the mixture is maintained.

10 gm. of propylene glycol and 60 cc of purified water are mixed together and heated to 75—80°C. The aqueous solution is then poured into the oil phase with vigorous agitation to emulsify.

Agitation is continued until the temperature drops down to 48°C. Sufficient water is added to the emulsion to weigh 94.5 gm. Agitation is continued at a slow rate for congealing. Stirring is stopped when temperature reaches 42°C. 0.5 gm of steroid is homogeneously dispersed in 5 gm of propylene glycol and 20 gm of the cream is added and mixed thoroughly. The remainder of the cream is added and mixed until homogeneous (for about half an hour) to form the cream of the invention.

Example 11

Topical Cream

21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1) (all-in-solution)	0.025 gm.
Econazole Nitrate	1.0 gm.
Castor Oil, U.S.P.	1.0 gm.
Petrolatum, U.S.P.	8.0 gm.
Promulgen, Type D	14.0 gm.
Silicone DC 200 Fluid	1.0 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid is dissolved in castor oil with gentle heat not over 90°C. Petrolatum and Promulgen D are melted, mixed with silicone oil and heated to 80—85°C and then mixed in the castor oil solution.

10 gm. of propylene glycol is dissolved in 57 cc. of purified water and heated to 80—85°C. The hot aqueous solution is added to the oil phase with vigorous agitation to emulsify. The mixture is cooled to 55°C, and sufficient water is added to make 94 gm. The mixture is mixed at a slow rate until the temperature drops to 42°C. The econazole nitrate is homogeneously dispersed in 5 gm of propylene glycol and the resulting dispersion is incorporated into the above cream and mixed well.

Example 12

Topical Cream

21 - chloro - 9 - fluoro - 2',3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b][1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1) (all-in-solution)	0.1 gm.
Castor Oil, U.S.P.	4.0 gm.
Nystatin	2.0 gm.
Petrolatum, U.S.P.	4.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid is dissolved in castor oil with gentle heat not over 90°C, and BHT is added with mixing to dissolve. Petrolatum and Promulgen D are melted and heated to 80—85°C, silicone oil added thereto, and the mixture is incorporated into the castor oil portion. 10 gm. of propylene glycol is dissolved in 55 cc of water and heated to 80—85°C and poured into the oil phase with vigorous agitation to emulsify. Mixing is continued until the temperature drops down to 48°C. Sufficient water is added to make 93 gm and mixing is continued at a slow rate until the temperature of the congealed cream drops down to 42°C. Nystatin is dispersed in 5 gm of propylene glycol and incorporated into the cream by thorough mixing for about 20—30 minutes.

Example 13

Lotion, 0.025% (all-in-solution)

9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide	0.025 gm.
Castor Oil, U.S.P.	5.0 gm.
Petrolatum, U.S.P.	1.2 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	3.0 gm.
Butylated Hydroxytoluene (BHT)	0.020 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid and BHT are dissolved in castor oil with gentle heat not over 90°C. The petrolatum and Promulgen are melted together and heated to 75—80°C and then mixed with the steroid-BHT solution. The resulting mixture is added to a hot 75—80°C mixture of propylene glycol in 75 cc of purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48°C. Sufficient hot (48—50°C) purified water is then added to make 100 gm. Mixing is then continued at a slow rate until the temperature of the cream reaches 42°C.

Example 14

Lotion, 0.025% (biphasic)

9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide	0.025 gm.
Castor Oil, U.S.P.	3.0 gm.
Petrolatum, U.S.P.	1.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	3.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

0.0125 gm of the steroid and BHT are dissolved in castor oil with gentle heat not over 90°C. Petrolatum and Promulgen D are melted together, heated to 75—80°C and mixed with the steroid-BHT mixture. The resulting mixture is added to a hot 75—80°C mixture of 10 gm propylene glycol in 75 cc of purified water with vigorous agitation to emulsify. Agitation is continued until the temperature drops down to 48°C and sufficient hot (48—50°C) purified water is added to make 94 gm. Agitation is continued at a slow rate until the temperature reaches 45°C and a congealed cream forms. The remainder of the steroid is dispersed homogeneously in 5 gm of propylene glycol. 10 gm of the congealed cream is added to the steroid-glycol mix with thorough mixing until homogeneous. The remainder of the congealed cream is then added as well as sufficient water to make 100 gm and the mixture is mixed for about half an hour until a homogeneous lotion is formed.

Example 15

Topical Cream, 0.1% (all-in-solution)

9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide	0.1 gm.
Castor Oil, U.S.P.	12.5 gm.
Petrolatum, U.S.P.	4.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol Monostearate	0.3 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid, propylene glycol monostearate and BHT are dissolved in castor oil with gentle heat, not over 90°C. Petrolatum and Promulgen D are melted together, and silicone fluid is added. After mixing, the mixture is added to the castor oil solution with thorough mixing, maintaining the temperature at 75—80°C. Propylene glycol is mixed in 59 cc of water and heated to 80°C to form the aqueous phase which is added with vigorous agitation to the oil phase to emulsify. Agitation is continued until the temperature drops down to 48°C. Sufficient 50°C water is added to make 100 gm. Mixing is continued at a slow rate to congeal the mixture until the temperature drops down to 42°C.

Example 16

Topical Cream, 0.1% (biphasic)

9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide	0.1 gm.
Castor Oil, U.S.P.	5.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.
Propylene Glycol Monostearate	0.3 gm.
Petrolatum, U.S.P.	5.0 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol	15.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Purified Water, sufficient to make	100.0 gm.

0.05 gm of the steroid is dissolved in castor oil with gentle heat not over 90°C. BHT and propylene glycol monostearate are added and the mixture is heated to dissolve all solids. Petrolatum and Promulgen D are melted, mixed together and heated to 75—80°C. The two oil liquids are then mixed together with silicone oil and the temperature of the mixture is maintained.

10 gm. of propylene glycol and 60 cc of purified water are mixed together and heated to 75—80°C. The aqueous solution is then poured into the oil phase with vigorous agitation to emulsify.

Agitation is continued until the temperature drops down to 48°C. Sufficient water is added to the emulsion to weigh 94.5 gm. Agitation is continued at a slow rate for congealing. Stirring is stopped when temperature reaches 42°C. 0.5 gm of steroid is homogeneously dispersed in 5 gm of propylene glycol and 20 gm of the cream is added and mixed thoroughly. The remainder of the cream is added and mixed until homogeneous (for about half an hour) to form the cream of the invention.

Example 17

Topical Cream

9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide (all-in-solution)	0.025 gm.
Econazole Nitrate	1.0 gm.
Castor Oil, U.S.P.	3.0 gm.
Petrolatum, U.S.P.	8.0 gm.
Promulgen, Type D	14.0 gm.
Silicone DC 200 Fluid	1.0 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid is dissolved in castor oil with gentle heat not over 90°C. Petrolatum and Promulgen D are melted, mixed with silicone oil and heated to 80—85°C and then mixed in the castor oil solution.

10 gm. of propylene glycol is dissolved in 57 cc. of purified water and heated to 80—85°C. The hot aqueous solution is added to the oil phase with vigorous agitation to emulsify. The mixture is cooled to 55°C, and sufficient water is added to make 94 gm. The mixture is mixed at a slow rate until the temperature drops to 42°C. The econazole nitrate is homogeneously dispersed in 5 gm of propylene glycol and the resulting dispersion is incorporated into the above cream and mixed well.

Example 18

Topical Cream

9α - fluoro - 11β,16α,17,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide (all-in-solution)	0.1 gm.
Castor Oil, U.S.P.	12.5 gm.
Nystatin	2.0 gm.
Petrolatum, U.S.P.	4.0 gm.
Promulgen, Type D—(PEG fatty alcohol ether)	10.0 gm.
Butylated Hydroxytoluene	0.02 gm.
Silicone Fluid DC 200, 350 cps.	1.0 gm.
Propylene Glycol	15.0 gm.
Purified Water, sufficient to make	100.0 gm.

The steroid is dissolved in castor oil with gentle heat not over 90°C, and BHT is added with mixing to dissolve. Petrolatum and Promulgen D are melted and heated to 80—85°C., silicon oil added thereto, and the mixture is incorporated into the castor oil portion. 10 gm. of propylene glycol is dissolved in 55 cc of water and heated to 80—85°C and poured into the oil phase with vigorous agitation to emulsify. Mixing is continued until the temperature drops down to 48°C. Sufficient water is added to make 93 gm and mixing is continued at a slow rate until the temperature of the congealed cream drops down to 42°C. Nystatin is dispersed in 5 gm of propylene glycol and incorporated into the cream by thorough mixing for about 20—30 minutes.

WHAT WE CLAIM IS:—

1. A composition for topical application in the form of a cream or lotion, comprising at least one steroid, selected from 21 - chloro - 9α - Δ^4 - pregnene - 11β,16α,17α - triol - 3,20 - dione 16,17-acetonide; 21 - chloro - 9 - fluoro - 2' 3' - dihydro - 11β - hydroxy - 5' - phenylpregna - 1,4 - dieno[16α,17-b] - [1,4]dioxin - 3,20 - dione: dichloro methane solvate (1:1), and 9α - fluoro - 11β,16α,17,21 - tetrahydroxy - pregna - 1,4 - diene - 3,20 - dione 16,17-acetonide, a ricinoleate vehicle (as hereinbefore defined) in which said steroid is at least partially soluble, polyethylene glycol fatty alcohol ether as an emulsifier-thickener, an oleaginous material or emollient, a preservative and water.

2. The composition as defined in claim 1, wherein said ricinoleate vehicle is castor oil.

3. The composition as defined in claim 1 or 2, further including one or more antioxidants.

4. The composition as defined in claim 1, 2 or 3, wherein said steroid is present in an amount of from 0.005 to 0.6% by weight of the composition, said ricinoleate

vehicle is present in an amount of from 0.5 to 20% by weight of the composition, said emulsifier-thickener is present in an amount of from 1 to 14% by weight of the composition, said oleaginous material or emollient is present in an amount of from 0.2 to 8% by weight of the composition, said preservative is present in an amount of from 8 to 50% by weight of the composition, and said water is present in an amount of from 30 to 90% by weight of the composition.

5. A composition as defined in claim 1, 2 or 3, in the form of a cream wherein said steroid is all-in-solution, and said steroid is present in an amount of from 0.005 to 0.6% by weight of the composition, said ricinoleate vehicle is present in an amount of from 0.5 to 16% by weight of the composition, said emulsifier-thickener is present in an amount of from 5 to 14% by weight of the composition, said oleaginous material or emollient is present in an amount of from 2 to 8% by weight of the composition, said preservative is present in an amount of from 10 to 50% by weight of the composition, and said water is present in an amount of from 30 to 70% by weight of the composition, and optionally including an anti-oxidant present in an amount of from 0.005 to 0.04% by weight of the composition, and further optionally including an anti-whitening agent or anti-foaming agent present in an amount of from 0.2 to 3% by weight of the composition.

6. A composition as defined in claim 1, 2 or 3, in the form of a cream of the biphasic type, wherein said steroid is present in an amount of from 0.005 to 0.6% by weight of the composition, said ricinoleate vehicle is present in an amount of from 0.5 to 14% by weight of the composition, said emulsifier-thickener is present in an amount of from 8 to 12% by weight of the composition, said oleaginous material or emollient is present in an amount of from 2 to 8% by weight of the composition, said preservative is present in an amount of from 10 to 50% by weight of the composition, and said water is present in an amount of from 30 to 70% by weight of the composition, and optionally including an anti-oxidant present in an amount of from 0.005 to 0.04% by weight of the composition, and further optionally including an anti-whitening agent or anti-foaming agent present in an amount of from 0.2 to 3% by weight of the composition.

7. A composition as defined in claim 1, 2 or 3, in the form of a lotion wherein said steroid is all-in-solution, said steroid is present in an amount of from 0.005 to 0.6% by weight of the composition, said ricinoleate vehicle is present in an amount of from 0.5 to 16% by weight of the composition, said emulsifier-thickener is present in an amount of from 5 to 14% by weight of the composition, said oleaginous material or emollient is present in an amount of from 0.5 to 6% by weight of the composition, said preservative is present in an amount of from 10 to 50% by weight of the composition, and said water is present in an amount of from 50 to 84% by weight of the composition, and optionally including an anti-oxidant present in an amount of from 0.005 to 0.04% by weight of the composition, and further optionally including an anti-whitening agent or anti-foaming agent present in an amount of from 0.2 to 3% by weight of the composition.

8. A composition as defined in claim 1, 2 or 3 in the form of a lotion of the biphasic type, wherein said steroid is present in an amount of from 0.005 to 0.6% by weight of the composition, said ricinoleate vehicle is present in an amount of from 0.5 to 14% by weight of the composition, said emulsifier-thickener is present in an amount of from 1 to 5% by weight of the composition, said oleaginous material or emollient is present in an amount of from 0.2 to 5% by weight of the composition, said preservative is present in an amount of from 8 to 50% by weight of the composition, and said water is present in an amount of from 50 to 90% by weight of the composition, and optionally including an antioxidant present in an amount of from 0.005 to 0.04% by weight of the composition, and further optionally including an anti-whitening agent or anti-foaming agent present in an amount of from 0.2 to 3% by weight of the composition.

9. A composition as defined in any one of the preceding claims wherein said oleaginous material is petrolatum and said preservative is propylene glycol and optionally including butylated hydroxytoluene as an antioxidant and further optionally including a silicone fluid and propylene glycol monostearate.

10. A composition as defined in any one of the preceding claims further including econazole, nystatin, neomycin, gramicidin or mixtures thereof.

11. A method of treating dermatitis in non-human creatures which comprises administering topically an effective amount of a composition as defined in any one of the preceding claims.

12. A composition as claimed in claim 1, substantially as herein described.

13. A composition as claimed in claim 1, substantially as given in any of the Examples.

14. A method as claimed in claim 11, substantially as herein described.

Agents for the Applicants,
STANLEY, POPPLEWELL, FRANCIS & ROSS,
1, Dyer's Buildings,
Holborn,
London EC1.
Chartered Patent Agents.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.