CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-535

PHARMACOLOGY REVIEW

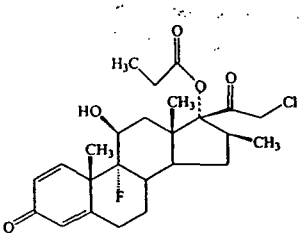
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-535
Review number: 1
Sequence number/date/type of submission: 000 / 27 September 2002 / original submission
Information to sponsor: Yes
Sponsor and/or agent: Galderma Laboratories
Manufacturer for drug substance: [redacted] or [redacted]

Reviewer name: Paul C. Brown
Division name: Division of Dermatologic and Dental Drug Products
HFD #540
Review completion date: March 20, 2003

Drug:

Trade name: Clobex
Generic name (list alphabetically): clobetasol propionate
Code name: 661.337
Chemical name: Pregna-1,4-diene-3,20-dione, 21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-, (11ß,16ß)-
CAS Registry Number: 25122-46-7
Molecular Formula/ Molecular Weight: $C_{25}H_{32}ClFO_5$ / MW=466.98
Structure:



Relevant INDs/NDAs/DMFs: IND 54,230

Drug Class: corticosteroid

Indication: corticosteroid responsive dermatoses

Clinical formulation:

Ingredient	% (w/w)
Clobetasol propionate, USP	0.05
Hydroxypropyl methyl cellulose, USP	[redacted]
PEG	[redacted]
Carbomer	[redacted]
Mineral Oil, USP	[redacted]
Propylene glycol, USP	[redacted]
Sodium Hydroxide, NF	[redacted]
Purified water	[redacted]

Route of administration: topical to the skin

Indication: corticosteroid-responsive dermatoses

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Introduction and drug history:
This NDA was submitted under section 505(b)(2) of the FD&C Act. It refers to the Agency's finding of safety and effectiveness for the approved product Temovate E Emollient Cream. The sponsor has conducted an HPA axis suppression study comparing their product with Temovate E Emollient Cream. Therefore, much of the pharmacology and toxicology support for the current NDA is derived from reference to the Agency's finding of safety and efficacy for the NDA for Temovate E Emollient Cream. The sponsor attended pre-IND, End-of-Phase 2 and pre-NDA meetings with the Division.

Studies reviewed within this submission:
None

Studies <u>not</u> reviewed within this submission:
The following studies are not reviewed in detail because they were previously reviewed in IND 54,230. The results of these studies are summarized in the appropriate sections below

<u>Reproductive and developmental toxicology:</u>

1. Preliminary study of embryo-fetal toxicity in the CD rat by dermal administration (1.CG.03.SRE.12055)
2. Study of embryo-fetal toxicity in the CD rat by dermal administration (1.CG.03.SRE.12081)

<u>Special toxicology studies:</u>

1. Acute dermal irritation test in the rabbit (1.CG.03.SRE.8274.GDL)
2. Acute eye irritation in rabbits (1.CG.03.SRE.12053)
3. Skin sensitization test in guinea pigs (1.CG.03.SRE.12054)
4. Thirteen-week topical range-finding study of clobetasol 0.05% lotion in hairless mice, with or without simulated sunlight (RDS.03.SRE.12258)

Executive Summary

I. Recommendations

A. Recommendation on Approvability
The application is approvable from a pharm/tox perspective provided the sponsor agrees to conduct the recommended phase 4 nonclinical studies.

B. Recommendation for Nonclinical Studies
It is recommended that the sponsor be asked to agree to conduct a dermal carcinogenicity study and an evaluation of the photocarcinogenic potential of the drug product as phase 4 commitments.

C. Recommendations on Labeling
Suggested wording for the nonclinical portions of the label is included at the end of the review.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings
The nonclinical studies conducted by the sponsor confirm that clobetasol propionate has teratogenic potential. A teratogenicity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities. Other nonclinical findings suggest that the lotion did not cause skin sensitization and was not irritating to the skin or eye.

B. Pharmacologic Activity
No new pharmacology information was provided by the sponsor.

C. Nonclinical Safety Issues Relevant to Clinical Use
No new safety issues relevant to clinical use have been identified in the studies conducted by the sponsor. The teratogenic potential of clobetasol propionate is addressed in the label.

III. Administrative

A. Reviewer signature: /S/

B. Supervisor signature: Concurrence - /S/

Non-Concurrence - _____
(see memo attached)

C. cc: list:
HFD-540/PM/Harris
HFD-540/Pharm. Tox. Sup./Jacobs
HFD-540/MO/Cook
HFD-540/Chem./Turujman
HFD-540/Div. Dir./Wilkin

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology summary:

Clobetasol propionate acts, as do other glucocorticoids, by binding to intracellular glucocorticoid receptors. The receptor/glucocorticoid complex interacts with other proteins and with glucocorticoid-response elements in various genes. This interaction alters the expression of these genes ultimately leading to changes in the levels of the corresponding proteins produced.

The physiologic alterations induced by glucocorticoids include stimulating the liver to produce glucose from amino acids and glycerol and stimulating glycogen deposition. Glucocorticoids inhibit glucose utilization peripherally, increase protein breakdown and activate lipolysis.

Glucocorticoids have anti-inflammatory and immunosuppressive activity. This is largely mediated through inhibition of inflammatory cell activity through numerous mechanisms of action including inhibition of the arachidonic acid cascade, depression of cytokine production and direct effects on lymphocytes.

Topical glucocorticoid products produce local changes in the skin including skin atrophy, telangiectasias and vasoconstriction. Clobetasol propionate products are generally among the most potent corticosteroid products as determined by vasoconstriction in the skin.

Pharmacology conclusions:

No new pharmacology information is included in the current NDA.

III. SAFETY PHARMACOLOGY:

Safety pharmacology summary:

The sponsor submitted a translation of a Japanese paper published in 1975 by Irie et al., which characterized a number of secondary pharmacology studies of clobetasol propionate. The findings of this paper are summarized below.

Neurological effects:

No particular effects were observed when mice were treated with 300 mg/kg by intraperitoneal injection in olive oil. At 500 mg/kg there were decreases in alertness, grooming, reactivity, touch response, pain response, reflexes and limb tone. One of three animals given 300 mg/kg and 2 of 3 animals given 500 mg/kg died 6 days after dosing.

A 500 mg/kg dose also transiently decreased spontaneous locomotor activity approximately 20 minutes after dosing.

A subcutaneous dose of clobetasol propionate (200 mg/kg) slightly reduced the writhing reaction of mice to an intraperitoneal dose of 0.6% acetic acid. Lower doses of clobetasol propionate had no effect.

Intraperitoneal doses of clobetasol propionate of 100 and 200 mg/kg produced a slight prolongation of pentobarbital induced sleep time in mice (33 and 51% longer than control, respectively).

Subcutaneous clobetasol propionate at a dose of 100 mg/kg did not inhibit strychnine sulfate or pentetrazol-induced convulsions in mice.

Intravenous clobetasol propionate at a dose of 10 mg/kg appeared to produce some alterations in the spontaneous EEG of rabbits. EEG was generally inhibited during the first 25 minutes after administration with the EEG becoming irregular in the hippocampus and with the amygdala displaying high voltage slow waves. This period of inhibition was followed by a period of arousal until 60 minutes after administration.

Cardiovascular effects:
Doses of clobetasol propionate of up to 7 mg/kg given intravenously did not alter the ECG or blood pressure of anesthetized rabbits compared to control administration of the acetone vehicle. In addition, clobetasol propionate at doses of up to 70 µg/kg did not alter the elevation of blood pressure induced by epinephrine or norepinephrine or the blood pressure decrease induced by acetylcholine in this model.

The motility of isolated perfused guinea pig heart preparations were not affected by treatment with 100 µg of clobetasol propionate.

Clobetasol propionate did not appear to cause any increase in local capillary permeability after the intracutaneous injection of a 10 mg/mL solution of the drug in olive oil. Increased capillary permeability was determined by the presence of blue exudate at the location of the injection due to leakage of trypan blue, which had been intravenously injected immediately after the intracutaneous administration of the clobetasol propionate.

Pulmonary effects:
Respiration was not altered in the anesthetized rabbit by intravenous doses of clobetasol propionate of up to 7 mg/kg.

Renal effects:
Urine volume was measured in rats and mice over five hours after subcutaneous injection of clobetasol propionate at doses of 50 and 200 mg/kg. Clobetasol propionate at both doses increased urine volume during this time in both mice and rats. The increase in urine volume was as much as 7 fold higher than control in mice and as much as 22 fold higher in rats.

Gastrointestinal effects:
The spontaneous motility of isolated guinea pig ileum or isolated rabbit small intestine preparations was not altered by clobetasol propionate at concentrations of up to 100 mg/mL or 100 µg/mL, respectively. The response of the isolated guinea pig ileum to acetylcholine, nicotine, histamine, serotonin and $BaCl_2$ was also not altered.

Other:
The spontaneous motility of the isolated rat uterus was not altered by clobetasol propionate at concentrations of up to 100 mg/mL.

The effect of clobetasol propionate on contraction of the isolated rat diaphragm as triggered by electrical stimulation of the diaphragmatic nerve was assessed. A concentration of 1 µg/mL did not influence the diaphragm contraction.

An anaphylaxis provocation test with clobetasol propionate was conducted in guinea pigs. Guinea pigs were administered clobetasol propionate by subcutaneous injection into the forelimb armpit (5 mg/animal) and then the animals received two weekly subcutaneous injections of 10 mg/animal. Three weeks after the start of the injections a challenge dose of 16 mg was given intravenously. No anaphylactic reaction was observed.

Safety pharmacology conclusions:
No new safety pharmacology studies have been conducted by the sponsor.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK summary:
Nonclinical studies in animals or in *in vitro* Franz Chambers have shown that clobetasol propionate is absorbed through animal and human skin. Different formulations can have different absorption characteristics. Generally, percutaneous absorption of clobetasol propionate is increased by occlusion. Clearance of clobetasol propionate is mainly by the liver, bile and feces.

The sponsor conducted a human skin *in vitro* liberation-penetration study with their lotion in comparison to Temovate E Emollient Cream and Temovate Cream. This study showed that clobetasol propionate penetrated in to the epidermis and dermis from all three formulation although the sponsor's lotion produced a statistically greater concentration in these tissues compared to the other two formulations. None of the formulations produced clobetasol propionate levels above the limit of quantification in the receptor fluid during the 16 hour experiment.

The clinical studies conducted by the sponsor confirm that systemic exposure to clobetasol occurred from topical use of the lotion since adrenal suppression was observed.

PK/TK conclusions:
The studies conducted by the sponsor confirm that clobetasol propionate is absorbed from the lotion in sufficient amounts to cause local and systemic effects.

IV. GENERAL TOXICOLOGY:

Toxicology summary:
No general toxicology studies have been conducted with the clobetasol propionate lotion formulation. The toxicity of clobetasol propionate has been characterized in a number of nonclinical studies with a variety of formulations conducted primarily by Glaxo Wellcome and

submitted to the FDA in their NDAs for Temovate products. The current NDA refers to the Agency's finding of safety and efficacy for Temovate. There are also several reports of nonclinical investigations of clobetasol propionate toxicity available in the literature. The studies clearly show that the topical application of clobetasol propionate can produce pronounced systemic exposures and effects typical of corticosteroids.

The NDAs for Temovate and published reports on clobetasol toxicity include 3 and 6 month subcutaneous toxicity studies in rats and a 3 month subcutaneous toxicity study in dogs. Topical studies in the rat have been conducted with various formulations for up to 3 months and in the rabbit for up to 3 weeks. Conclusions from the review of these studies by Dr. Syed Alam are quoted below from his review of NDA 19-322.

> "The adverse effects reported in the subacute and chronic (6-month) toxicity studies (dermal and SC) were of the type usually associated with long-term potent steroid therapy. These include emaciation, thinning of the skin and retardation of hair growth at the application site, increases in serum SGOT and SGPT values, decreased plasma cortisol levels, involution of the thymus, adrenal atrophy, localized hepatic necrosis, hyperglycemia and lymphopenia. The incidence and severity of these effects were significantly greater when the drug was administered SC than when administered topically. The steroid is probably a potent immunosuppressant, since bronchial and lung infections were rather rampant among the treated animals, resulting in considerable number of deaths, particularly in the high-dose groups. By the SC route, a maximum tolerated dose of the drug substance in the rat appears to be 20 µg/kg/day. When the drug substance was applied topically, a "no-effect" dose was 2.5 µg/kg/day and 1 gm/kg/day of 0.05% P-C cream appears to have no significant toxic effects in this species. This is about 14x the proposed maximum clinical dose per day."

The established clinical use of corticosteroids has identified the following adverse effects of other clobetasol propionate products. These local reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. In rare instances, treatment (or withdrawal of treatment) of psoriasis with corticosteroids is thought to have exacerbated the disease or provoked the pustular form of the disease, so careful patient supervision is recommended. Because of the high potency of clobetasol propionate, the use of topical clobetasol is generally limited to two weeks of use except in some cases four weeks are permitted for the treatment of small areas of severe psoriasis.

Toxicology conclusions:
No new general toxicology information has been submitted by the sponsor.

V. GENETIC TOXICOLOGY:

Genetic toxicology summary:
Mutagenicity studies have been performed with clobetasol by Glaxo and submitted in NDA 19-322. Clobetasol was negative for mutagenicity in the Ames test, the yeast gene conversion assay and the bacterial DNA fluctuation test.

Genetic toxicology conclusions:
No new genetic toxicology studies have been submitted at this time.

Labeling recommendations:
The sponsor included the wording shown below in their proposed labeling. This is identical to wording used in other recently approved clobetasol propionate products and is acceptable.

> Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

VI. CARCINOGENICITY:

Carcinogenicity summary:
The carcinogenic potential of clobetasol propionate has not been previously assessed.

Carcinogenicity conclusions:
Recommendations for further analysis: The sponsor was not told that an evaluation of the carcinogenic potential of their product was recommended. It was previously concluded that if the duration of product use was limited then an evaluation of its carcinogenic potential may not be necessary. The proposed label of the product states that for the treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses treatment should be limited to 2 consecutive weeks except in the treatment of moderate to severe plaque-type psoriasis in which case the product can be applied to —— body surface area for up to 4 consecutive weeks. This label does not exclude repeated treatment but only advises against using the product for more than 2 or 4 consecutive weeks. Therefore, the product could be used repeatedly in a nonconsecutive manner for a total of more than 2 or 4 weeks. One of the indications for this product is psoriasis. Psoriasis is a chronic condition that is not cured by corticosteroid treatment and often requires repeated long-term treatment. The Division has recommended dermal carcinogenicity evaluations for other topical corticosteroids used for the treatment of psoriasis. Consequently, it may be appropriate to recommend that the sponsor evaluate the dermal carcinogenicity of clobetasol propionate. Since there are other approved topical clobetasol propionate products on the market it may be acceptable for the sponsor to conduct this evaluation after approval. This would be consistent with the Division's recent recommendations to other sponsors of topical corticosteroid products (For example, for IND —— and IND ——, which are both topical clobetasol products.)

Labeling Recommendations:
Until adequate studies are conducted, the wording shown below, as proposed by the sponsor is acceptable.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicology summary:

Clobetasol, like other corticosteroids, is teratogenic in animals even when administered at relatively low doses. Reproductive toxicity studies with clobetasol were conducted by Glaxo and by a Japanese group. The results of these studies have been reviewed in the NDAs submitted by Glaxo for their clobetasol products. The results are summarized here.

Segment I studies in rats showed no effect on fertility and no effects in males, while females showed slightly increased fetal resorption and decreased live offspring at 0.05 mg/kg. Clobetasol was teratogenic in mice at the lowest dose tested (0.03 mg/kg) when administered subcutaneously. In rats, the subcutaneous administration of 0.4 mg/kg was teratogenic. Maternal toxicity and fetotoxicity were observed at the 0.1 and 0.4 mg/kg dose in rats. At the 0.4 mg/kg dose in rats, neonate pups did not thrive and were found to be underweight and immature. No effects were observed in second generation rat litters. Segment III studies in rats of subcutaneously administered clobetasol showed effects on the behavior of the dams and the condition of the pups immediately after birth at doses of 0.05 and 0.1 mg/kg, but growth of the pups thereafter was considered normal.

Two developmental toxicity studies have been conducted by the sponsor:

Preliminary study of embryo-fetal toxicity in the CD rat by dermal administration (1.CG.03.SRE.12055)

Study of embryo-fetal toxicity in the CD rat by dermal administration (1.CG.03.SRE.12081)

These studies were submitted to IND 54,230 in 1999 in SN 008 and were previously reviewed. These studies showed that clobetasol propionate lotion applied during gestation days 6-17 in the rat caused maternal toxicity at all doses used (1 mL/kg of 0.005%, 0.015% or 0.05% or 0.05, 0.15 and 0.5 mg/kg). Fetal survival was reduced by the 0.015 and 0.05% concentrations of clobetasol propionate. Dose-related abnormalities were observed in the fetuses. There was an effect on fetal growth with treated groups showing low fetal weights, reduced skeletal ossification and umbilical herniation. The dose related reduction in ano-genital distance and displaced testes observed in male fetuses may be due to an effect of the clobetasol propionate on the androgen-dependent nature of these parameters. Some of the abnormalities, such as cleft palate, are commonly observed in teratogenicity studies with corticosteroids.

Reproductive and developmental toxicology conclusions:

The studies conducted by the sponsor confirm the teratogenic potential of clobetasol propionate and should be summarized in the label.

Labeling recommendations:

The following wording is proposed by the sponsor to describe a rat fertility study in the Carcinogenesis, Mutagenesis, Impairment of Fertility section of the label:

The following wording is recommended to be more consistent with the Temovate labels.

> Studies in the rat following subcutaneous administration at dosage levels up to 50 µg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

The sponsor proposes the following wording for the Pregnancy section of the label:

> **Pregnancy:** ***Teratogenic Effects: Pregnancy Category C:*** Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.
>
> Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.
>
> Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. Abnormalities seen included cleft palate and skeletal abnormalities.
>
> In rabbits, clobetasol propionate was teratogenic at doses of _____. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.
>
> A teratogenicity study in rats using the dermal route resulted in dose related maternal and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. _____
>
> There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobetasol Propionate Lotion, 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

This proposed wording is similar to other recently approved topical clobetasol propionate drug products although some of the animal dose information appears to be removed. This wording also includes a paragraph describing the new information from the topical teratogenicity study in rats conducted by the sponsor. This wording is generally acceptable although it is recommended that the animal dose information and animal to human dose comparisons be replaced or added. This will make the label more consistent with the reference Temovate drugs. The proper dose ratios have been calculated based on the maximum recommended weekly dose of product specified in the label of 50 g. These calculations are shown in an Appendix attached at the end

of this review. Also a more complete description of the abnormalities found in the rat dermal teratogenicity study is recommended.

The following wording is suggested:

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 µg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

A teratogenicity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobetasol Propionate Lotion, 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

VIII. SPECIAL TOXICOLOGY STUDIES:

Summary of special toxicology studies:

A skin irritation study in rabbits was submitted to IND 54,230 (Report No.1.CG.03.SRE.8274.GDL). This study tested the 0.05% clobetasol propionate lotion and its vehicle. The test materials (0.5 mL) were applied to the nonabraded skin of rabbits under occlusion for 4 hours. No irritation was noted at 1, 24, 48 or 72 hours after removal of the dressing.

An acute eye irritation study was submitted to IND 54,230 (Report No. 1.CG.03.SRE.12053). This study showed that a single 0.1 mL dose of the 0.05% clobetasol propionate lotion was not irritating to the eyes of rabbits at 24, 48 or 72 hours after administration.

A skin sensitization study in guinea pigs was submitted to IND 54,230 (Report No. 1.CG.03.SRE.12054). Guinea pigs were induced with 9 doses (3/week) of the lotion under occlusion for 6 hours for each dose. After 10 days a 24 hour occluded challenge dose was administered. No reaction was observed so the lotion was considered to be non-sensitizing.

The sponsor conducted a thirteen-week topical range-finding study of clobetasol 0.05% lotion in hairless mice with or without simulated sunlight (Report No. RDS.03.SRE.12258). This study was also submitted to IND 54,230 (SN 025). This study showed that all three volumes of the 0.05% clobetasol lotion applied (25, 50 and 100 µL) produced thinning of the skin, weight loss and death in male and female mice when treated for 13 weeks. The report concluded that none of the treatments would be acceptable for a photocarcinogenicity study since even the smallest volume (25 µL) applied only 3 times per week was still significantly toxic. The presence or absence of UV irradiation did not appear to make much difference in the skin effects and mortality induced by the lotion. Clobetasol treatment appeared to decrease the skin thickening induced by UV possibly due to the atrophogenic effects of the corticosteroid. However, this study was not conclusive on whether clobetasol lotion altered other possible effects of UV in the skin. The clobetasol lotion appeared to have no effect on the wrinkling induced by UV. Erythema in this study was minimal and appeared to be caused by the clobetasol lotion and not by UV. The anti-inflammatory and vasoconstrictive activity of clobetasol may make erythema less useful as a marker of UV damage in this case.

Conclusions:
It appears that it would not be possible to conduct a photocarcinogenicity study with 40 weeks of treatment with 25-100 µL of the 0.05% lotion. However, the use of exposures below those expected clinically is acceptable for a carcinogenicity or photocarcinogenicity study if that is the only way to obtain a tolerated treatment. The sponsor previously noted that corticosteroids might offer protection from UV-induced skin cancer. However, the possible protective effects of corticosteroids in cancer development do not appear to be well established in the literature. Therefore, it seems appropriate for the sponsor to further investigate the photocarcinogenic potential of clobetasol lotion. One possibility would be for the sponsor to conduct a new range finding study with lower concentrations of clobetasol and if necessary use a treatment regimen of only 3 times per week in order to see if this regimen would be feasible for a photocarcinogenicity assay. Another possibility would be to conduct a shorter study than a traditional photocarcinogenesis assay but include analyses of alternative endpoints that are markers of UV-induced skin damage.

Note: These recommendations about the evaluation of the photocarcinogenic potential of the drug were forwarded to the sponsor under IND 54,230 on March 14, 2003.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

If the medical reviewer finds that the clinical studies establish a sufficient clinical bridge to the approved product then the NDA is approvable from a pharmacology and toxicology perspective. It is recommended that the sponsor be asked to agree to conduct a dermal carcinogenicity study and an evaluation of the photocarcinogenic potential of the drug as phase 4 commitments.

Other Toxicology Issues:
Polyoxyethylene glycol 300 isostearate (polyethylene glycol 300 isostearate, [redacted] is a noncompendial ingredient. It is not clear if this exact excipient has been used in other approved drug products. However, other very similar compounds have been used in approved drug products. It seems unlikely that the relatively minor differences between this compound and other members of this class of compounds would produce significantly different biological effects. Completion of photocarcinogenicity and dermal carcinogenicity studies will help characterize this compound.

Recommendations:
It is recommended that the following agreements be made with the sponsor and that these agreements be included in any approval letter.

1. The Applicant commits to performing dermal carcinogenicity testing of the drug product.

   Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 6 months of the date of the approval of the protocol
Final Report Submission:	Within 12 months after the study completion

2. The Applicant commits to a study to evaluate the effects of the drug product on UV-induced skin cancers.

   Commitment Category: NON-CLINICAL TOXICOLOGY

Protocol Submission:	Within 4 months of the date of this letter
Study Start:	Within 6 months of the date of the approval of the protocol
Final Report Submission:	Within 12 months after the study completion

Recommended Labeling:
The following wording is recommended for the nonclinical sections of the label.

Carcinogenesis, mutagenesis, impairment of fertility:
Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Studies in the rat following subcutaneous administration at dosage levels up to 50 µg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C.
Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 µg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

A teratogenicity study in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day of Clobetasol propionate. These doses are approximately 0.14 to 1.4 times, respectively, the human topical dose of Clobetasol Propionate Lotion, 0.05%. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobetasol Propionate Lotion, 0.05% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

X. APPENDIX/ATTACHMENTS:

References reviewed:

Irie D, Sumiyama H, Uchiyama T. General pharmacology of clobetasol 17-propionate (SN-201) a new synthetic corticosteroid. J. Med. Soc. Toho, Japan 1975 22(3-4):318-331.

Calculation of maximum human dose of clobetasol propionate per day:

50 g lotion per week = approximately 7.1 g lotion per day

7.1 g lotion/day x 0.05% clobetasol propionate = 3.6×10^{-3} g clobetasol propionate/day

= 3.6 mg clobetasol propionate/day

$$\frac{3.6 \text{ mg clobetasol propionate/day}}{60 \text{ kg person}} = 0.06 \text{ mg clobetasol propionate/kg/day}$$

0.06 mg clobetasol propionate/kg/day x 37 (Km) = 2.22 mg clobetasol propionate/m^2/day

Human to animal dose comparison based on body surface area.

Dose in mg/kg	Dose in mg/m^2 (mg/kg × *km*)	Multiple of human dose (mg/m^2 ÷ 2.22 mg/m^2)
Mouse (*km* = 3)		
1	3	1.4
0.03	0.09	0.04
Rabbit (*km* = 12)		
0.003	0.036	0.02
0.01	0.120	0.05
Rat (*km* = 6)		
0.05	0.3	0.14
0.5	3	1.4

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