CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-644

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-644**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**5/6/03**
DRUG NAME:	**Clobetasol Propionate**
INDICATION:	**moderate to severe forms of [redacted] scalp psoriasis**
APPLICANT:	**Galderma Laboratories, L.P.**
DOCUMENTS REVIEWED:	**Vol. 1.1-1.2, 1.10-1.14**
REVIEW DIVISION:	**Division of Dermatologic and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Paul C. Brown, Ph.D.**
PHARM/TOX SUPERVISOR:	**Abby Jacobs, Ph.D.**
DIVISION DIRECTOR:	**Jonathan Wilkin, M.D.**
PROJECT MANAGER:	**Jacquelyn Smith**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability
The NDA is approvable from a pharm/tox perspective.

1.2 Recommendation for nonclinical studies
Additional phase 4 nonclinical studies are recommended. The Applicant should be asked to commit to perform dermal carcinogenicity testing of the drug product. The sponsor should also be asked to evaluate the potential of the drug product to modify UV-induction of skin cancers. This might be evaluated by examining appropriate markers of UV exposure or UV damage in skin. If the clinical and biopharmaceutics reviewers find measurable systemic absorption or systemic effects in human studies then the Applicant should be asked to commit to conduct a nonclinical study to evaluate the impact of clobetasol propionate on fertility.

1.3 Recommendations on labeling
Several changes to the label are recommended. Since this NDA does not rely on the Agency's finding of efficacy and safety for another approved drug product, the label can not contain information from other approved drugs unless that information is available publicly or the Applicant has obtained the right to refer to it. Recommended wording for the nonclinical sections of the label is included at the end of the review.

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings
The Applicant has conducted only limited new nonclinical studies and instead relies significantly on the published literature for nonclinical information on clobetasol propionate.

The Applicant conducted a 13 week study in minipigs in which the animals were treated with topical clobetasol propionate 0.05% shampoo for 15 minutes a day. The animals showed hyperkeratosis, and epidermal and dermal atrophy at the site of treatment. These effects are typical of potent corticosteroids. Systemic exposure to clobetasol propionate was not detected at a limit of 0.2 ng/mL and no systemic toxicity was observed. The maximum dose applied was 2 mL/kg of the 0.05% shampoo, which corresponds to a total dose of clobetasol propionate of 1 mg/kg.

The Applicant included copies of published papers that describe studies conducted with clobetasol propionate in mice and rats. These studies utilized both subcutaneous and topical routes and included one, three and six month studies. Common findings included atrophy of the thymus, spleen and adrenal glands. Lung abcesses were frequently observed. White blood cells and lymphocytes were often decreased and neutrophils increased. The effects observed in rats were reversible after 1 to 2 months recovery. Most of the effects observed in these studies appear to be manifestations of the HPA axis suppressive and immunosuppresive effects of clobetasol propionate. These effects are common with corticosteroids.

2.2 Pharmacologic activity

The Applicant did not submit any new information on the pharmacologic activity of clobetasol propionate. As a corticosteroid, the primary mechanism of action of clobetasol propionate is through receptor mediated changes in gene expression. Physiologic effects of 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. 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.

2.3 Nonclinical safety issues relevant to clinical use

There are no significant safety issues relevant to the clinical use, particularly considering that clobetasol propionate has been used in humans before. However, additional nonclinical studies are recommended as phase 4 commitments since the applicant has not addressed the impact of clobetasol propionate on fertility and since the carcinogenic and photocarcinogenic potential of clobetasol propionate has not been evaluated.

PHARMACOLOGY/TOXICOLOGY REVIEW

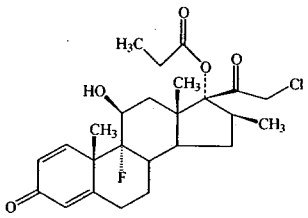
3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-644
Review number: 1
Sequence number/date/type of submission: 000 / 6 May 2003 / original submission
Information to applicant: Yes (X) No ( )
Applicant and/or agent: Galderma Laboratories, L.P.
Manufacturer for drug substance: [redacted]

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

Drug:

Trade name: Clobex Shampoo
Generic name: clobetasol propionate, 0.05% shampoo
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 60,934 (Galderma)

Drug class: corticosteroid

Indication: treatment of moderate to severe forms of [redacted] scalp psoriasis

Clinical formulation:

Ingredient	Function	Percent Formula % (w/w)
Clobetasol propionate	Active	0.05
Alcohol, USP	[redacted]	[redacted]
Cocobetaine		
Sodium laureth-2 sulfate		

Polyquaternium-10	[redacted]	[redacted]
Sodium citrate dihydrate, USP		
Citric acid monohydrate, USP		
Purified water, USP		

Route of administration: topical

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:
This NDA was submitted under section 505(b)(2) of the FD&C Act. Much of the nonclinical information has been submitted as copies of published literature. The Applicant also submitted several study reports.

Pharmacokinetics/toxicokinetics:

1. Plasma levels of clobetasol 17-propionate in rats following single topical application of clobetasol 0.05% shampoo (0.05%, w/w) and Dermovate Scalp (0.05%, w/w) (Report No: RDS.03.SRE.4706, also referred to as 1.CG.03.SRE.4706)

Repeat dose toxicity:

1. A four week dermal dose range finding study in minipigs (Report No.: 1.CG.03.SRE.12249)
2. A 13 week dermal toxicity study in minipigs (Report No.: 1.CG.03.SRE.12252)

Studies not reviewed within this submission:
The following studies are not reviewed in detail because they were previously reviewed in IND [redacted] IND 60,934. The results of these studies are summarized in the appropriate sections below

Pharmacokinetics/toxicokinetics:

1. Comparison of the *in vitro* liberation-penetration of clobetasol 17-propionate applied as two different formulations onto human skin (Report No. 1.CG.03.SRE.4651)

Reproductive and developmental toxicology:

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)

Special toxicology studies:

1. Acute dermal irritation in rabbits (Report No. 1.CG.03.SRE.12140)
2. Acute eye irritation in rabbits (Report No. 1.CG.03.SRE.12139)
3. Skin sensitization test in guinea pigs (Buehler test; 3 applications) (Report No. 1.CG.03.SRE.12152) *Note: A preliminary study (1CG.03.SRE.12141) was also submitted to this NDA, but will not be further reviewed since this preliminary study was only used to select the doses for the subsequent sensitization study, which was already reviewed.*

Two other studies are referred to in the NDA. These two studies are genotoxicity studies of clobetasol propionate that were conducted by another applicant ([redacted] but Galderma has obtained permission to refer to these studies from [redacted] These studies were submitted to [redacted] and were reviewed. These studies will not be reviewed in detail here but will be summarized below.

3.2 PHARMACOLOGY

3.2.1 Brief 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.

3.2.2 Primary pharmacodynamics

Mechanism of action:
The applicant did not submit any papers on the mechanism of action of clobetasol propionate. Corticosteroids bind to receptors that can alter the expression of a variety of genes in target cells. This altered gene expression is thought to be responsible for many of the actions of corticosteroids. Inhibition of phospholipase A2, cyclooxygenase and nitric oxide synthase by corticosteroids decreases the production of prostanoids, platelet activating factor and nitric oxide, which play important roles in mediating the inflammatory response. Corticosteroids decrease the production and release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. Corticosteroids also decrease leukocyte extravasation and migration. Additional mechanisms may be relevant, as well.

Drug activity related to proposed indication:
The topical anti-inflammatory activity of clobetasol has been tested in several animal models. Clobetasol has been shown to be more potent than hydrocortisone and less potent than halobetasol in decreasing croton oil-induced ear swelling in mice and rats, in decreasing UV-induced dermatitis in guinea pigs and in decreasing immune-mediated dermatitis in oxazalone-sensitized rats (Yawalakar et al., 1991). Ear edema in mice sensitized to picryl chloride was also reduced by topical application of clobetasol propionate (Bäck and Egelrud, 1985).

Yawalakar et al. (1991) also demonstrated the antiproliferative activity of clobetasol propionate by showing that cotton pellets impregnated with clobetasol propionate induce less granuloma formation than control cotton pellets. However, the clobetasol propionate induced a greater degree of systemic effects (thymus atrophy) than did a halobetasol propionate dose that gave a

similar suppression of granuloma formation. The antiproliferative activity of clobetasol propionate was also demonstrated in guinea pigs using hexadecane-induced skin hyperplasia. Marshal and du Vivier (1978) showed that clobetasol propionate decreased epidermal DNA synthesis after topical treatment.

3.2.3 Secondary pharmacodynamics

Corticosteroids act primarily through the glucocorticoid receptor. Other sites of action have not been identified. Adverse effects from topical corticosteroid use are often due to undesirable pharmacological activity at systemic sites. One of the most significant of these effects is the suppression of adrenal function, which is triggered by the suppression of the hypothalamic-pituitary-adrenal axis. The pituitary is stimulated by the hypothalamus to secrete ACTH, which in turn stimulates the adrenal glands to produce cortisol. Cortisol has a negative feedback effect on the hypothalamus and leads to a suppression of pituitary ACTH release and subsequent decrease in adrenal activity. Exogenous steroids can also have a negative feedback effect on the hypothalamus, which can lead to adrenal suppression. This can be particularly severe in the case of exogenous corticosteroids since they may be much more potent than endogenous corticosteroids.

3.2.4 Safety pharmacology

The applicant 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 was 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.

3.2.5 Pharmacodynamic drug interactions

The potential for drug interactions does not appear to have been assessed for clobetasol propionate.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief 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.

3.3.3 Absorption

Study title: Plasma levels of clobetasol 17-propionate in rats following single topical application of clobetasol 0.05% shampoo (0.05%, w/w) and Dermovate Scalp (0.05%, w/w)

Study No: RDS.03.SRE.4706, also referred to as 1.CG.03.SRE.4706 (This also incorporates the bioanalytical study report No. RDS.03.SRE.4490.)
Volume #13, and page #1458
Conducting laboratory and location: Galderma R&D, Sophia Antipolis, France
Date of study initiation: 5 October 2001
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: clobetasol 0.05% shampoo, batch No. PLG-1. The shampoo was assayed and found to contain —— of the nominal amount of clobetasol propionate. The purity of the clobetasol propionate used to formulate the shampoo was not provided. Dermovate Scalp was a Japanese commercial formulation, batch No. DC3C1.

Methods:
Dosing:
Hair on the backs of male Sprague-Dawley rats was clipped on an area of approximately 15 cm^2. Animals were sedated with i.p. Diazepam (4 mg/kg) and anesthetized with isoflurane before application of the test materials. A ring of inert material was glued with cyanoacrylate glue to the skin. A single dose of test material 0.6 ml/kg (clobetasol dose of 0.3 mg/kg) was applied in the test ring and massaged for about 5 seconds. The test site was covered with a non-occlusive bandage. Animals were fitted with a collar to prevent ingestion of the test substances. The shampoo was washed off after 15 or 30 minutes and the Dermovate was washed off after 10 hours. The treatment groups were as follows:

Group	Treatment	Duration of treatment	No. of animals
A	Clobetasol 0.05% shampoo	15 min	12
B	Clobetasol 0.05% shampoo	30 min	12
C	Dermovate Scalp	10 hr	12
D	Untreated	NA	2

Pharmacokinetic sampling: Blood was collected from 4 animals per time point at 0.5, 1, 2, 3, 4, 6, 8, 10, 17, 24 and 48 hours after drug application. For groups B and C the 0.5 and 10 hours

blood samples, respectively, were collected before the treatment site was washed. One sample was taken from each untreated rat in group D at the beginning of the study. Clobetasol 17-propionate was measured by HPLC MS/MS with a limit of quantification of ——

Clinical signs: Local irritation was assessed at 15 and 30 minutes after drug application.

Results:
Clinical signs: No signs of irritation were noted.
Pharmacokinetics: Blood levels of clobetasol propionate were frequently (63 to 70% of the samples) below the limit of quantification in the shampoo treated animals, whereas clobetasol propionate was quantifiable in all of the samples taken from Dermovate treated animals. Treatment of animals with the shampoo for 15 or 30 minutes produced similar pharmacokinetic parameters. The mean C_{max} was from 0.55 to 1.06 ng/mL for the shampoo treated animals and was 2.83 for the Dermovate treated animals. T_{max} was similar in all cases and was between 0.5 and 1 hours. The mean $AUC_{0\text{-}48h}$ was from 3 to 15 ng·h/mL for the shampoo treated animals and was 45 ng·h/mL for the Dermovate Scalp treated animals.

Individual Study Conclusions:
Clobetasol propionate is absorbed in the rat from 15 or 30 minute application of the 0.05% shampoo. Although, as expected, the amount absorbed from the relatively short exposure period with the shampoo is generally less than that absorbed from a much longer exposure (10 hour) to Dermovate Scalp solution.

The applicant also conducted an *in vitro* human skin liberation-penetration study with a 0.05% clobetasol propionate shampoo formulation (Report No. 1.CG.03.SRE.4651). This study was previously reviewed in IND 60,934. When approximately 10 mg of the shampoo was applied to 1 cm^2 skin samples for 15 minutes, 0.002 µg clobetasol propionate was recovered in the epidermis. This was equal to approximately 0.06% of the applied dose. When the application period was extended to 16 hours, approximately 0.81 µg clobetasol propionate was recovered in the epidermis (approximately 16% of the applied dose). At either duration, the amount of clobetasol propionate in the dermis was below the limit of quantification and was —— in the receptor fluid. For comparison, the penetration of clobetasol propionate into the epidermis from a 16 hour application of Temovate® Scalp Application was approximately 0.32 µg or 7% of the applied dose. Clobetasol propionate penetration from the shampoo appears to be slightly greater than from Temovate® Scalp application when applied for equal times. However, the intended use of the shampoo is for 15 minute applications followed by rinsing. This application method appears to result in substantially less absorption of clobetasol propionate.

3.3.4 Distribution
The applicant has not assessed the distribution of clobetasol propionate.

3.3.5 Metabolism
The applicant has not assessed the metabolism of clobetasol propionate. The applicant submitted a literature reference that demonstrates that topical treatment of mouse skin with corticosteroids, including clobetasol propionate, induces drug-metabolizing enzymes in the skin (Finnen et al.

1984). This paper does not identify specific enzymes but the CYP1A1/2 enzymes are likely to be involved.

3.3.6 Excretion

The applicant has not assessed the excretion of clobetasol propionate.

3.3.7 Pharmacokinetic drug interactions

The applicant has not assessed the pharmacokinetic drug interactions of clobetasol propionate.

3.3.10 Tables and figures to include comparative TK summary

Not applicable.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology:
The applicant completed a 4 week dose range finding study of the shampoo in minipigs and a 13 week dermal toxicity study in minipigs. Minipigs treated for up to 13 weeks with topical clobetasol propionate 0.05% shampoo for 15 minutes a day showed hyperkeratosis, and epidermal and dermal atrophy at the site of treatment. These effects are typical of potent corticosteroids. Systemic exposure to clobetasol propionate was not detected at a limit of 0.2 ng/mL and no systemic toxicity was observed. The maximum dose applied was 2 mL/kg of the 0.05% shampoo, which corresponds to a total dose of clobetasol propionate of 1 mg/kg.

The applicant has also included copies of published papers that describe studies conducted with clobetasol propionate in mice and rats. These studies utilized both subcutaneous and topical routes and included one, three and six month studies. Most of the effects observed in these studies appear to be manifestations of the HPA axis suppressive and immunosuppresive effects of clobetasol propionate. For example, common findings included atrophy of the thymus, spleen and adrenal glands. Lung abscesses were frequently observed. White blood cells and lymphocytes were often decreased and neutrophils increased. The effects observed in rats were reversible after 1 to 2 months recovery.

The established clinical use of corticosteroids has identified the following adverse effects of other clobetasol propionate products. These local reactions are listed in 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.

Genetic toxicology:
The applicant has right of reference to two genotoxicity studies. These studies were reviewed in IND —. Clobetasol propionate did not produce any increase in chromosomal aberrations in Chinese hamster ovary cells *in vitro* at doses up to 4670 µg/mL in the presence or absence of metabolic activation. Clobetasol propionate was also negative in the micronucleus test in mice after oral doses of up to 2000 mg/kg.

Carcinogenicity:
The carcinogenicity of clobetasol propionate has not been evaluated.

Reproductive toxicology:
Fertility:
The applicant has not supplied any information on the effect of clobetasol propionate on fertility.

Embryofetal toxicity:
The applicant conducted a preliminary study (1.CG.03.SRE.12055) and a main study (1.CG.03.SRE.12081) of the embryofetal toxicity of topical clobetasol propionate lotion in CD rats. These studies were submitted to IND —. The preliminary study found that dose related toxicity of clobetasol propionate was observed at all dose levels used regardless of the whether the material was occluded or unoccluded. Both occluded and non-occluded females had fetuses with abnormalities that were likely to be due to the clobetasol propionate. Animals treated without occlusion but with Elizabethan collars had higher exposure levels and the report concludes that this may have been due to some oral ingestion of the clobetasol propionate in these animals. This may translate into greater effects for these animals since, for example, the non-occluded animals had lower fetal survival. The report recommended that exposures in the main study should be conducted for 6 hours with occlusion to reduce possible oral exposure. In addition, the report recommended that dose volumes be reduced to 1 ml/kg and that the lowest concentration of clobetasol propionate used be reduced to 0.005% and the highest concentration remain at 0.05%.

In the main embryofetal toxicity study, CD rats received drug (0.005, 0.015 and 0.05% lotion) daily from day 6 to day 17 of gestation. Animals received drug 6 hours per day with occlusive dressing. The topically applied clobetasol propionate caused maternal toxicity at all doses used in the study. Fetal survival was reduced for the 0.015 and 0.05% doses. 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. A dose related reduction in ano-genital distance and displaced testes was observed in male fetuses and 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.

Although these studies were not conducted with the shampoo formulation, use of the lotion formulation under occlusion for 6 hours appears to produce greater exposure to clobetasol propionate than a shorter treatment with the shampoo. Maximum blood levels of clobetasol propionate measured on gestation day 17 were 5.82, 12.80 and 48.4 ng/mL in the rats treated

with the 0.005, 0.015 and 0.05% lotions, respectively. This is greater than the C_{max} of [redacted] that was measured in rats treated with the 0.005% shampoo for 15 to 30 minutes (see Pharmacokinetics/toxicokinetics above).

Pre- and post-natal toxicity:
The applicant submitted a copy of a published paper on the effects of clobetasol propionate on the perinatal and lactation periods in rats (Kuramoto et al., 1977). This paper is reviewed in more detail in the Reproductive and developmental toxicity section (3.4.6) below. Briefly, clobetasol propionate at subcutaneous doses of 25, 50 and 100 µg/kg from day 17 of gestation to day 21 postpartum was maternally toxic. The body weight gain of the pregnant females was decreased by all doses of clobetasol propionate. Gestation was prolonged by the high dose and the number of delivered offspring overall and per female was reduced. During the perinatal period almost half of the offspring in the 100 µg/kg group died and about 7% of the offspring in the 50 µg/kg group died. Eye opening and hair appearance were delayed in the offspring but otherwise development appeared relatively normal. The reproductive performance and fertility of the F1 offspring and the development of the F2 offspring were not affected.

Human data:
Several epidemiologic studies of corticosteroid use in pregnancy have been published. Conclusions vary, but it appears that there may be an association of corticosteroid use in early pregnancy with some congenital anomalies. In particular, cleft lip and palate appear to be elevated in newborns from mothers using corticosteroids during the first months of gestation.

Special toxicology:
Since this drug is a new formulation for topical use on the scalp, the applicant conducted acute eye irritation, acute dermal irritation, and skin sensitization studies with the clobetasol propionate shampoo and the shampoo without the clobetasol propionate. These studies were submitted to IND 60,934 and previously reviewed. The clobetasol propionate shampoo was considered to be a slight skin irritant and the vehicle a skin irritant. Both the clobetasol propionate containing shampoo and placebo shampoo were slightly irritating to the eye when diluted to 30%. In the sensitization study, slight to moderate erythema was observed in almost all of the animals in the vehicle or clobetasol propionate treated group during the induction phase of the study. No reaction was observed after challenge with the clobetasol propionate shampoo or the vehicle shampoo. Therefore, neither the vehicle shampoo nor clobetasol propionate shampoo induced delayed hypersensitivity in guinea pigs.

3.4.2 Single-dose toxicity

Kuramoto et al. (1975a) assessed the acute toxicity of clobetasol propionate in mice and rats. Animals were given clobetasol propionate in a 0.04% Tween 80 suspension by the oral, subcutaneous and intraperitoneal routes. No animals died at the highest oral dose of 3 g/kg. Necropsy of the orally treated animals revealed yellow-brown kidneys and mild atrophy of the adrenal glands and spleen of the mice and adrenal atrophy, liver discoloration and hyperemia of the jejunum in the rats. The LD_{50} at day 21 for the subcutaneous route for was 81.7 mg/kg for both male and female mice and it was 397.3 and 365.8 mg/kg for male and female rats, respectively. The LD_{50} at day 21 for the intraperitoneal route for was 156.4 and 117.8 mg/kg for

male and female mice, respectively, and it was 413.7 and 351.3 mg/kg for male and female rats, respectively. Clinical signs and necropsy findings were similar for the animals treated by the subcutaneous and intraperitoneal routes and seemed to follow a dose response. Clinical signs included inactivity, closed eyes, piloerection, emaciation and hair loss. Necropsy findings included atrophy of the spleen, adrenal glands, testes, epididymides and ovaries, enlargement of the stomach and hyperemia of the small intestines.

3.4.3 Repeat-dose toxicity

Study title: A four week dermal dose range finding study in minipigs

Key study findings: Minipigs tolerated the daily 15 minute application of the clobetasol propionate 0.05% shampoo well over 28 days. Slight irritation was sometimes noted and this may be due to the vehicle. Decreased adrenal weights suggest that there may be some systemic effects of the clobetasol propionate.

Study No.: 1.CG.03.SRE.12249
Volume #11 and page #443
Conducting laboratory and location: [redacted]
Date of study initiation: 15 May 2000
GLP compliance: Yes
QA report: Yes
Drug, lot # and % purity: Clobetasol 0.05% w/w shampoo, batch 662.066/114003*9. The shampoo was assayed and found to contain [redacted] of the nominal amount of clobetasol propionate. The purity of the clobetasol propionate used to formulate the shampoo was not provided.

Methods

Doses:

Group	Treatment	Dose volume (mL/kg)	Dose clobetasol propionate (mg/kg)
1	Vehicle shampoo	2	0
2	Clobetasol propionate 0.05% shampoo	0.5	0.25
3	Clobetasol propionate 0.05% shampoo	1	0.5
4	Clobetasol propionate 0.05% shampoo	2	1.0

Species/strain: minipig/ [redacted]
Number/sex/group or time point (main study): 1/sex/group
Route, formulation and volume: topical, shampoo, volume as noted in table above
Satellite groups used for toxicokinetics or recovery: none
Age: 3-4 months
Weight: 5.7 to 6.7 kg
Unique study design or methodology: The test substance was applied topically for 28 days to an area of approximately 10% total skin surface area. The day before the first application and periodically during the study the hair was clipped from the treatment area. The test articles were applied for 15 minutes once per day and then washed off with water.

Observation times and results

Mortality: All animals survived until the end of the study.

Clinical signs: Well-defined erythema was observed on days 22 and 23 in the male receiving vehicle. The male receiving 2 mL/kg of the clobetasol shampoo had well defined erythema on days 19 to 21 and very slight erythema on days 22 to 24 and a scab on day 22 to 28.

Body weights: The female receiving the 2 mL/kg dose appeared to have lower weight gain but all other animals gained similar amounts of weight.

Food consumption: Some unconsumed food was observed for different animals during the study but this appears incidental.

Hematology: There were no clear drug-related effects.

Clinical chemistry: Not done.

Urinalysis: Not done.

Gross pathology:
No macroscopic findings were noted for any animal.

Organ weights:
There was a tendency toward lower adrenal gland weights in males and females and lower thymus weights in females with increasing dose of clobetasol propionate.

Group	Adrenal weights (g)		Thymus weights (g)	
	Males	Females	Males	Females
1 (vehicle)	1.15	0.98	6.02	12.07
2 (0.5 mL/kg)	1.12	1.04	11.89	11.76
3 (1 mL/kg)	1.08	0.88	10.54	8.17
4 (2 mL/kg)	0.92	0.77	11.98	6.26

The pituitary and spleen were also weighed but the weight of these organs was not clearly affected by the clobetasol propionate treatment.

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes ( ), no (x)
The only tissues examined were treated and untreated skin. This is adequate since this was a dose range finding study.

Focal crusts were noted at the treated site in both animals in group 2, the female in group 3 and the female in group 4. Focal crusts were also noted at untreated sites in the male in group 1 and the female in group 2. Focal edema of the epidermis was noted in the male in group 1.

Toxicokinetics: Not done.

Study title: A 13 week dermal toxicity study in minipigs

Key study findings: Minipigs treated for 13 weeks with topical clobetasol propionate 0.05% shampoo for 15 minutes a day showed hyperkeratosis, and epidermal and dermal atrophy at the site of treatment. These effects are typical of potent corticosteroids. Systemic exposure to clobetasol propionate was not detected at a limit of [redacted] and no systemic toxicity was observed.

Study No.: 1.CG.03.SRE.12252
Volume #11 and page #522
Conducting laboratory and location: [redacted]
Date of study initiation: 7 March 2001
GLP compliance: Yes
QA report: Yes
Drug, lot # and % purity: Clobetasol 0.05% w/w shampoo, batch 662.066/PLG-1. The shampoo was assayed and found to contain [redacted] of the nominal amount of clobetasol propionate. The purity of the clobetasol propionate used to formulate the shampoo was not provided.

Methods

Doses:

Group	Treatment	Dose volume (mL/kg)	Dose clobetasol propionate (mg/kg)
1	Vehicle shampoo	2	0
2	Clobetasol propionate 0.05% shampoo	0.5	0.25
3	Clobetasol propionate 0.05% shampoo	1	0.5
4	Clobetasol propionate 0.05% shampoo	2	1.0

Species/strain: minipig/ [redacted]
Number/sex/group or time point (main study): 4/sex/group
Route, formulation and volume: topical, shampoo, volume as noted in table above
Satellite groups used for toxicokinetics or recovery: none
Age: 3-4 months
Weight: 5.3 to 8.1 kg
Unique study design or methodology: The test substance was applied topically for at least 91 days to an area of approximately 10% total skin surface area. Three days before the first application and periodically during the study the hair was clipped from the treatment area. The test articles were applied for 15 minutes once per day and then washed off with water.

Observation times and results

Mortality: One female from group 3 was killed for humane reasons on day 1. The animal was injured during blood sampling. A replacement female was added to this group on day 2. All other animals survived until scheduled sacrifice.

Clinical signs: There were no treatment-related signs during the study. Occasional incidences of erythema and/or edema were observed but these were not clearly related to drug treatment. Some animals from all groups had decreased appetite during the first third of the study. These animals were given an alternate diet until their appetites returned.

Body weights: There were no significant differences in body weights or body weight gains between drug and vehicle treated animals throughout the study.

Food consumption: There were some decreases in food consumption noted in all groups, particularly during the times when animals exhibited decreased appetite.

Ophthalmoscopy: The following findings were noted before the start of treatment: one male in the vehicle group had pigmented spots on the posterior lens capsule of the right eye, one female in the vehicle group had an opacity of the anterior lens capsule of the right eye and one female in the vehicle group had an opacity on the posterior lens capsule of the right eye.

The following findings were noted prior to sacrifice: all of the findings noted before the start of treatment, plus one male in group 4 had pigmented spots on the posterior lens capsule, one male in group 4 had an opacity on the cornea and one female in group 4 had an opacity on the posterior lens capsule with a small cleft toward the cornea.

It is not clear that these findings are related to drug treatment since similar findings were noted in control as well as drug treated animals.

EKG: There were no statistically significant differences in the EKG parameters when the drug treated groups were compared to vehicle control treated animals.

Hematology: There were occasional group mean hematology values that were statistically significantly different in drug treated groups compared to control but none of these were clearly related to drug treatment since the changes were generally small and did not follow a dose response.

Clinical chemistry: The group mean cholesterol levels were lower in the clobetasol propionate treated males compared to control and this was a statistically significant difference in groups 2 and 4. These values were, however, within historical group mean control ranges. Other clinical chemistry changes do not appear to be drug related.

Urinalysis: There were no treatment-related findings.

Gross pathology: None of the few macroscopic changes were clearly related to drug treatment.

Organ weights: The relative heart weight was statistically higher in males in group 4 and the absolute liver weight was statistically higher in males in group 3. The relative brain weight was statistically higher in females in group 3. These findings do not appear to be related to drug

treatment since they do not follow a dose response or since they are within historical control ranges.

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes (x), no ( )
Skin changes were the only microscopic findings that were clearly related to drug treatment. Hyperkeratosis was observed in all animals including vehicle treated animals but it was more severe in the clobetasol propionate treated groups. Atrophy of the epidermis and dermis was not observed in the vehicle treated animals but it was observed in all clobetasol propionate treated animals and was most severe in group 4.

Toxicokinetics: Blood samples were taken for toxicokinetics on day 1 and day 88 prior to the daily treatment and at 1, 2, 4, 8 and 24 hours after the application of the test article. Clobetasol propionate was below the limit of quantitation [redacted] in all of the plasma samples obtained during the study.

Review of Applicant-submitted toxicology literature:
Kuramoto et al. (1975a) assessed the repeated dose toxicity of subcutaneously administered clobetasol propionate in Wistar rats given at doses of 6.25, 12.5, 25, 50 and 100 µg/kg for 3 months and 2.5, 5, 10, 20 and 40 µg/kg for 6 months. In the three month study animals showed emaciation, piloerection, rough hair and decreased motor activity at 25 µg/kg and higher after 3-4 weeks of treatment. All clobetasol propionate groups had decreased body weight gain through the study. Toxicity in the 100 µg/kg group was so severe that dosing was stopped in week 10. All of the females at 100 µg/kg died by the end of week 11 while 6 of 10 males at this dose died by the end of the study. One female in the 25 µg/kg group and one female in the 50 µg/kg group died during the study. The dead animals had abscesses and hepatization (solidification) in the lungs, atrophy of the thymus, spleen and adrenal glands, and mucus filled small intestines. Red blood cells tended to decrease in clobetasol treated animals while neutrophils increased and lymphocytes decreased. Clinical chemistry and urinalysis changes were generally not remarkable. Some relative organ weight increases were observed although these may be due to the decreased total body weight gains. However, thymus and adrenal gland weights were decreased. At necropsy, lung abscesses were observed especially in the males in the 50 and 100 µg/kg groups. Abscesses were also observed in the livers of some animals in the 25 and 50 µg/kg groups. Atrophy of the thymus and adrenal gland was observed even in the 6.25 µg/kg group. Microscopic examination showed that the lungs exhibited infiltration of neutrophils associated with necrosis and enlarged alveolar epithelium. Atrophy of the adrenal cortex was observed. Atrophy and decreased lymphocytes were observed in the thymus cortex.

In two other publications by Kuramoto et al. (1976a and 1976b), the reversibility of the effects observed after three months of subcutaneous treatment with clobetasol propionate were assessed at up to 2 months after cessation of treatment. Essentially all of the findings noted after three months of treatment were reversible.

Results of the six month subcutaneous rat study were similar to the 3 month study. Emaciation, hairloss and loose stool were observed at 20 µg/kg and higher. None of the animals died early in this study but all clobetasol propionate treated groups had dose-related lower weight gain

compared to control. Females in the 40 µg/kg group had decreased red blood cells. White blood cells were decreased in males at 10 µg/kg and higher and in females at 5 µg/kg and higher. Increased neutrophils and decreased lymphocytes were observed at 40 µg/mg. Clinical chemistry and urinalysis changes were generally not remarkable. Thymus weight decreased in females at doses of 5 µg/kg and higher and in males at 40 µg/kg. Spleen weight was decreased in males and females in a dose dependent fashion. Interestingly, adrenal weights were only significantly decreased in females at 20 and 40 µg/kg. At necropsy the thymic atrophy was noted but adrenal glands were grossly relatively normal. Upon microscopic examination, the thymic atrophy was observed and so were changes in the adrenal cortex such as atrophy and vacuolation. One male and one female in the 40 µg/kg group had focal necrosis in the liver. Hyaline casts were noted in the renal tubules of two males in the 40 µg/kg group. The red pulp of the spleen was enlarged in females in the 40 µg/kg group.

The toxicity of clobetasol propionate when applied topically to rats for one and three months was assessed in a published study by Kuramoto et al. (1975b). In these studies clobetasol propionate was tested in both cream and ointment formulations. The material was applied 6 days a week using 0.3 g for each application. Animals may have ingested some of the material. In the one month study 0.05% and 0.25% formulations were tested. In the one month study, emaciation, piloerection, lacrimation and decreased activity were observed. Eight of the female and one male rat receiving the 0.25% cream died during the 4 weeks. One female and one male receiving the 0.25% ointment died during the 4 weeks. Body weights and weight gains were decreased compared to control in all drug treated groups. White blood cells and lymphocytes were decreased and neutrophils increased in most clobetasol propionate treated groups. AST, ALT and ALP showed trends toward elevation in the clobetasol propionate treated animals. Organ weight decreases were observed in the thymus, spleen and adrenal glands. Thymus and adrenal gland atrophy was noted upon macroscopic examination of the animals treated with clobetasol propionate. Some animals receiving 0.25% clobetasol propionate had small hemorrhagic spots in the liver and white abscesses in the lungs. Microscopic examination showed atrophy of the adrenal cortex and atrophy and decreased lymphocytes in the thymus. Focal necrosis was observed in the livers of most animals in the 0.25% groups.

Only the 0.05% concentration of clobetasol propionate in the cream and ointment formulation was tested in the 3 month study. Clinical findings were similar to the one month study. Body weight gain was decreased by clobetasol propionate treatment compared to control. Three females receiving the clobetasol propionate ointment and one female receiving the clobetasol propionate cream died during the study. Red and white blood cells decreased slightly in the males receiving clobetasol propionate. An increase in neutrophils and decrease in lymphocytes was observed in the clobetasol propionate treated groups. Thymus weight was decreased in clobetasol propionate treated animals. Thymus size was decreased upon macroscopic examination. Lung abscesses were noted in the clobetasol propionate treated animals. Upon microscopic examination, it was noted that follicles were atrophied in the spleen of two females treated with the 0.05% clobetasol propionate cream. Mild vacuolation of the adrenal glands was noted in the cortex cells of the 0.05% cream group. Mild atrophy was noted in the thymus of clobetasol propionate treated animals.

Shimo et al. (1982) studied the topical application of a variety of corticosteroids, including clobetasol propionate, to rats. They showed that clobetasol propionate in an ointment at a dose of 0.125 mg/kg produced decreases in body weight and decreases in thymus, spleen and adrenal weights when applied for 30 days. White blood cells and lymphocytes decreased while neutrophils and red blood cells increased. Atrophy of the thymus, spleen, adrenal and skin at the treated site was observed macroscopically and microscopically. Atrophy of the mesenteric lymph nodes was also noted microscopically. These findings were found to be reversible after a 35 day recovery period.

3.4.4. Genetic toxicology

No new genotoxicity information was submitted in this NDA. The applicant has right of reference to two genotoxicity studies submitted by [redacted] These studies were reviewed in IND [redacted] These studies are summarized in the Overall toxicology summary (Section 3.4.1) above.

3.4.5. Carcinogenicity

The carcinogenic potential of clobetasol propionate has not been evaluated. The Division recommended that the carcinogenic and photocarcinogenic potential of the drug product be evaluated as phase 4 studies (see section 3.6 Overall Conclusions and Recommendations).

3.4.6. Reproductive and developmental toxicology

Review of Applicant-submitted reproductive and developmental toxicology literature:

Peri- and post-natal toxicity:

The applicant submitted a paper on the reproductive effects of clobetasol propionate when given during the perinatal and lactation periods in rats (Kuramoto et al., 1977). This paper was originally published in Japanese and the applicant has included an English translation in the NDA. Clobetasol propionate was administered to pregnant females subcutaneously at doses of 25, 50 and 100 µg/kg from day 17 of gestation to day 21 postpartum. Pregnant females were allowed to delivery naturally. The F0 females were sacrificed after the offspring were weaned at 4 weeks. Some of the offspring were sacrificed at 4 weeks and some were permitted to grow to 10 weeks at which time they were mated to test for effects on fertility and on the F2 generation. The body weight gain of the pregnant females was decreased by all doses of clobetasol propionate. There was a mean 1 day increase in gestation in the 100 µg/kg group. F0 females had dose-dependent decreases in adrenal gland weight. The females also had decreased spleen and liver weights in the 50 and 100 µg/kg groups and decreased thymus weight in the 100 µg/kg group. Upon microscopic examination, adrenal gland and thymus atrophy was noted. The number of delivered offspring overall and per female in the 100 µg/kg group was about half the number in control group even though the number of implantations was similar. During the perinatal period almost half of the offspring in the 100 µg/kg group died and about 7% of the offspring in the 50 µg/kg group died. Eye opening and hair appearance were delayed about one week in the 100 µg/kg offspring. Vision, hearing and equilibrium tests and weight gain were similar in offspring from clobetasol propionate treated and control groups. At four weeks of age, male F1 offspring had significant increase in spleen weight and slight increases in heart and thymus weight compared to control. Other organ weight changes appeared to be unrelated to treatment. Sperm count and morphology, estrus state and pregnancy rate in mated F1 animals

was essentially the same in the control and clobetasol propionate treated groups. Body weight gain in the F1 females during pregnancy was the same in the different groups. There were delays in ossification in the F2 fetuses. This was observed in all groups although there may have been a slightly greater number of fetuses with delayed ossification in the clobetasol propionate treated groups. The growth of the F2 offspring was similar in the clobetasol propionate and control groups.
It appears that clobetasol propionate administered perinatally can be embryotoxic and can reduce survival of newborns. The effects of clobetasol propionate do not appear to persist in the F1 generation, however, since they developed normally and were fertile.

Human data:
The applicant submitted two published papers on the teratogenic potential of corticosteroids in humans. Fraser and Sajoo (1995) surveyed the literature from 1952-1994 for reports of maternal treatment with corticosteroids during the first 70 days after conception. They identified 18 case reports in which mothers were exposed to corticosteroids during the first trimester. There were 26 exposed pregnancies of which 7 (27%) resulted in malformed offspring. They state that this is much greater than the usual population rate of 3%. Four of these malformations were for cleft palate. The authors also found 17 reports of series of patients, which included 457 exposed patients. In these series 16 or 3.5% malformations were noted, which is similar to the usual population rate. Two of these were cleft palate, which is greater than the expected number of 0.2 (1/2,500). Other malformations observed included anencephaly, clubfoot, dislocated hip, coarctation of the aorta, transposition of the great vessels, cataract, hypospadias, and undescended testis. The authors note that although the rate of malformations in the case reports was greater than the normal rate in the population, this is likely higher since adverse outcomes are more likely to be reported. The authors conclude that although the data is scanty and subject to bias, it suggests that there is little human teratogenic risk from corticosteroids. The particular corticosteroids listed in the paper include cortisone, cortisol, prednisone, prednisolone and dexamethasone. It appears that other corticosteroids were not surveyed.

The other paper (Czeizel and Rockenbauer, 1997) evaluated the teratogenic potential of oral and topical corticosteroids during pregnancy in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities. This data set contained 20,830 malformed cases and 35,727 healthy control births. Oral corticosteroid use was found to be 1.55% among the malformed cases and 1.41% among the healthy controls. Topical corticosteroid ointment use was found to be 0.35% among the malformed cases and 0.33% among the healthy controls. Examination of specific types of malformations showed that ear abnormalities were increased in the births from mothers treated with oral corticosteroids with an odds ratio of 3.07 (95% CI=1.73-5.45). The authors suggest that this may be actually due to the fact that these births were often pre-term and of low birth weight. Both oral and topical corticosteroid use during the first month of gestation were associated with an increased risk of cleft lip with or without cleft palate (odds ratio for oral use 5.88, 95% CI=1.70-20.32; odds ratio for topical use 4.19, 95% CI=1.47-11.97). In addition, oral corticosteroid use during the first month of gestation was associated with an increased risk of multiple abnormalities (odds ratio 4.88, 95% CI=1.41-16.88) and topical use during the first month was associated with an increased risk of neural tube defects (odds ratio 3.30, 95% CI=1.00-10.88). The authors suggest that the cleft lip and palate formation may not be due to corticosteroid exposure since the association was seen only with corticosteroid

use during the first month of gestation. They suggest that the first month of gestation comprise the 2 weeks before conception through pre-implantation and implantation. They suggest that this is prior to the critical period for formation of abnormalities. Overall, the authors concluded that treatment with corticosteroids in pregnancy presents little teratogenic risk to the fetus.

Other epidemiologic studies of corticosteroid and pregnancy outcome have been published but are not included in the NDA. For example, a study by Carmichael and Shaw (1999) examined the association between congenital anomalies and corticosteroid use during the period 1 month before to 3 months after conception. They found corticosteroid use was associated with an increased risk of cleft lip with and without cleft palate (odds ratio 4.3, 95% CI=1.1-17.2) and cleft palate (odds ratio 5.3, 95% CI=1.1-26.5). They concluded that there was an association between cleft lip and palate and corticosteroid use in early pregnancy.

None of the above human studies listed clobetasol propionate as one of the corticosteroids in the databases.

3.4.7 Local tolerance

The applicant previously submitted studies on the skin and eye irritation potential of the shampoo formulation with and without clobetasol propionate to IND 60,934. These studies are summarized in the Overall toxicology summary (Section 3.4.1) above.

3.4.8 Special toxicology studies

The applicant previously submitted a study on the sensitization potential of the shampoo vehicle and clobetasol propionate containing shampoo to IND 60,934. Neither the vehicle shampoo nor clobetasol propionate shampoo induced delayed hypersensitivity in guinea pigs.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
The NDA can be approved from a pharm/tox perspective. Several changes to the label are recommended. The approval letter should include the phase 4 commitments outlined below.

[redacted]

Carcinogenicity and photocarcinogenicity:
At the Pre-NDA meeting the applicant was told that the Division considers the treatment of psoriasis as a chronic indication. Consequently, it is recommended that the carcinogenicity and photococarcinogenicity of drugs used to treat psoriasis be evaluated even if the drug product is used in an intermittent manner. The applicant was told that these studies could be conducted post-approval. The applicant was asked to submit in the NDA their plans to evaluate carcinogenicity and photococarcinogenicity, including a timeline for fulfilling these phase 4 commitments. In a submission to IND 60,934 the applicant requested that the carcinogenicity and photocarcinogenicity be waived. The applicant listed several reasons for this request but overall the reasons were not considered convincing. The applicant was asked in the Filing Review letter to agree to evaluate carcinogenicity and photococarcinogenicity as Phase 4 commitments and to agree to a timeline for completion.

Excipients:
The drug product contains three excipients (cocobetaine, sodium laureth sulfate and Polyquaternium-10) that do not appear to be used in any approved prescription drug products. The applicant included reviews of the safety information available for each of these compounds. All appear to be widely used in cosmetic products. These three compounds do not appear to have been assessed for reproductive and developmental toxicity. Cocobetaine and sodium laureth sulfate have not been fully assessed for genotoxicity. Polyquaternium-10 and cocobetaine do not appear to have been tested for carcinogenicity. In spite of the lack of nonclinical studies of these compounds it may be reasonably safe to permit approval of the NDA, since these compounds are widely used and have been used in the 3 month minipig study and the clinical studies. The CDER guidance on nonclinical evaluation of excipients says that existing human data for some excipients can substitute for nonclinical safety data and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies. The cocobetaine and sodium laureth sulfate are surfactants and probably would not be very amenable to in vitro genotoxicity studies. Therefore, qualification of these excipients would be sufficient if they are included in a dermal carcinogenicity study. The applicant was told in the Filing Review Letter that the excipients were not fully qualified and that including them in a dermal carcinogenicity study would be sufficient to qualify them.

Recommendations:
It is recommended that the following agreements be made with the applicant 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 evaluate the potential of the drug product to modify UV-induction of skin cancer. This might be evaluated by examining appropriate markers of UV exposure or UV damage in the skin (see CDER Photosafety Testing Guidance).

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

If the clinical and biopharm reviewers find that significant systemic absorption or effects occur in human studies then the following phase 4 commitment should also be included in any approval letter.

3. The Applicant agrees to conduct a nonclinical study to evaluate the impact of clobetasol propionate on fertility.

Commitment Category: NON-CLINICAL TOXICOLOGY

Study Start:	Within 10 months of the date of this letter
Final Report Submission:	Within 12 months after the study completion

Suggested labeling:
The following wording is recommended for the nonclinical sections of the label. This wording differs somewhat from the wording suggested for the label of the clobetasol propionate lotion product recently submitted to the agency by Galderma (NDA 21-535). The lotion NDA was a 505(b)(2) NDA that referred to the Agency's finding of safety and efficacy for the approved product Temovate E Emollient Cream. Consequently, the label of the Galderma lotion was similar to the Temovate label. Since the current NDA for the shampoo is not referring to the Agency's finding of safety and efficacy for an approved product, the labeling can not include wording from studies only found in the Temovate NDA. The labeling below includes animal to human dose comparisons based on a maximum human use of 10 mL of the shampoo per day (see appendix for calculations).

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

Clobetasol propionate did not produce any increase in chromosomal aberrations in Chinese hamster ovary cells *in vitro* in the presence or absence of metabolic activation. Clobetasol propionate was also negative in the micronucleus test in mice after oral administration.

Studies of the effect of Clobex Shampoo on fertility have not been conducted.

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.

A teratogenicity study of clobetasol propionate in rats using the dermal route resulted in dose related maternal toxicity and fetal effects from 0.05 to 0.5 mg/kg/day. These doses are approximately 0.1 to 1.0 times, respectively, the maximum human topical dose of clobetasol propionate from Clobex Shampoo. Abnormalities seen included low fetal weights, umbilical herniation, cleft palate, reduced skeletal ossification other skeletal abnormalities.

Clobetasol propionate administered to rats subcutaneously at a dose of 0.1 mg/kg from day 17 of gestation to day 21 postpartum was associated with prolongation of gestation, decreased number of offspring, increased perinatal mortality of offspring, delayed eye opening and delayed hair appearance in surviving offspring. Some increase in offspring perinatal mortality was also observed at a dose of 0.05 mg/kg. Doses of 0.05 and 0.1 mg/kg are approximately 0.1 and 0.2 fold the maximum human topical dose of clobetasol propionate from Clobex Shampoo.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. Clobex Shampoo should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Signatures:

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

3.7. APPENDIX/ATTACHMENTS

List of published literature submitted in the NDA and reviewed:

Bäck O, Egelrud T. Topical glucocorticoids and suppression of contact sensitivity. Br. J. Dermatol., 1985, 112:539-545.

Czeizel A, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. Teratology, 1997, 56:335-340.

Finnen MJ, Herdman ML, Shuster S. Induction of drug metabolising enzymes in the skin by topical steroids. J. Steroid Biochem., 1984, 20(5):1169-1173.

Fraser FC, Sajoo A. Teratogenic potential of corticosteroids in humans. Teratology, 1995, 51:45-46.

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.

Kuramoto M, Ishimura Y, Morimoto J, Lee S-Y, Okubo T. Study on the toxicity of clobetasol 17-propionate: acute toxicity by oral, subcutaneous and intraperitoneal applications and subacute and chronic toxicities by subcutaneous applications in rats. Shikoku Igaku Zhassi, 1975a, 31 (6):377-398.

Kuramoto M, Ishimura Y, Morimoto J, Lee S-Y, Okubo T. Study on the toxicity of clobetasol 17-propionate: toxicities of clobetasol 17-propionate by percutaneous successive one and three month applications in rats. Shikoku Igaku Zhassi, 1975b, 31 (6):399-416.

Kuramoto M, Ishimura Y, Lee S-Y, Takeda K, Shigemi F, Tanaka M, Matsuura H. Study on the toxicity of clobetasol 17-propionate: recovery test against clobetasol 17-propionate. Shikoku Igaku Zhassi, 1976a, 32 (3):284-300.

Kuramoto M, Ishimura Y, Lee S-Y, Takeda K, Shigemi F, Tanaka M, Ai S, Matsuura H, Hiraga K, Shimpo K. Study on the toxicity of clobetasol 17-propionate: electron microscopic findings on the recovery of the tissue changes after daily subcutaneous injection of clobetasol 17-propionate in rats for a 3 month period consecutive. Shikoku Igaku Zhassi, 1976b, 32 (6):429-435.

Kuramoto M, Tanaka M, Ai S, Shigemi F, Takeda K, Oguro S, Matsuura H. Study on the effect of clobetasol 17-propionate on reproduction: effect of administering during perinatal and lactation periods in rats. Kiso To Rinsho, 1977, 11(1):17-36.

Marshal RC, du Vivier A. The effects on epidermal DNA synthesis of the butyrate esters of clobetasone and clobetasol and the propionate ester of clobetasol. Br, J. Dermatol., 1978, 98:355-359.

Shimo T, Takahara Y, Noguchi Y, Mukawa A, Kato H, Ito Y. Comparative toxicity test of dexamethasone valerate (DV-17) and other steroid ointments in rats. J. Toxicol. Sci., 1982, 1:15-33.

Yawalakar S, Wiesenberg-Boettcher I, Gibson JR, Siskin SB, Pignat W. Dermatopharmacologic investigations of halobetasol propionate in comparison with clobetasol 17-propionate. J. Am. Acad. Dermatol., 1991, 25(6):1137-44.

The following paper was not submitted by the applicant but was mentioned in the review: Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am. J. Med. Genetics, 1999, 86:242-244.

Calculation of maximum human dose of clobetasol propionate per day:

Ten mL of shampoo was used in at least one phase 2 study for treatment of patients with long hair and the maximum amount used in the pivotal clinical studies was approximately 9 mL. Therefore, the maximum dose is assumed to be approximately 10 mL shampoo per day, which equals approximately 10 g shampoo per day.

10 g shampoo/day x 0.05% clobetasol propionate = 5 x 10^{-3}g clobetasol propionate/day
= 5 mg clobetasol propionate/day

$$\frac{5 \text{ mg clobetasol propionate/day}}{60 \text{ kg person}} = 0.08 \text{ mg clobetasol propionate/kg/day}$$

0.08 mg clobetasol propionate/kg/day x 37 (Km) = 2.96 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 ÷ 2.96 mg/m^2)
Rat (*km* = 6)		
0.05	0.3	0.1
0.1	0.6	0.2
0.5	3	1.0

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/s/

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