CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-142

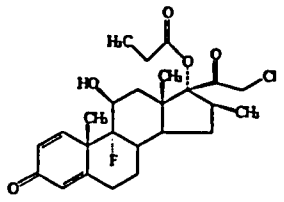
PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: corticosteroid
Reviewer Name: Paul C. Brown
Division Name: Division of Dermatologic and Dental Drug Products
HFD#540
Review Completion Date: December 7, 1999
Review number: 1 DEC - 7 1999
NDA number: 21-142
Serial number/date/type of submission: July 28, 1999 / original submission
Information to sponsor: revised labeling
Sponsor (or agent): Connetics Corporation
Manufacturer for drug substance: [redacted]

Drug:

Generic Name: Clobetasol propionate
Trade Name: Olux™ (proposed)
Chemical Name: (11ß,16ß)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17(1-oxopropoxy)-pregna-1,4-diene-3,20-dione
CAS Registry Number: 25122-46-7
Molecular Formula/ Molecular Weight: $C_{25}H_{32}ClFO_5$ / 466.98
Structure:



Relevant INDs/NDAs/DMFs: [redacted]
Drug Class: corticosteroid
Indication: [redacted]

Clinical formulation: topical foam containing 0.05% clobetasol propionate

Ingredient	% w/w
Clobetasol Propionate, USP	0.05
Dehydrated Alcohol (Ethanol) USP	[redacted]
Cetyl Alcohol, NF	[redacted]
Stearyl Alcohol, NF	[redacted]
Polysorbate 60, NF	[redacted]
Propylene Glycol, USP	[redacted]
Purified Water, USP	[redacted]
Citric Acid Anhydrous, USP and Potassium Citrate, USP	[redacted]

Route of administration: Topical to the scalp

Previous clinical experience: This product has not been previously used as formulated; however, clobetasol propionate is in several approved drug products and the foam vehicle is used in an approved betamethasone valerate product from the same sponsor.

Introduction and drug history:
The sponsor has submitted this NDA under section 505(b)(2) of the FD&C Act and is referring to the approved NDAs for clobetasol propionate as evidence of the safety for this drug (NDAs 19-322, 19-323, 19-966, 20-337 and 20-340). These NDAs are all for topical formulations containing 0.05% clobetasol propionate and were submitted by Glaxo. The sponsor has submitted the pharmacology and toxicology reviews of these NDAs in the nonclinical pharmacology and toxicology section of the current NDA. They have also included copies of translations of several papers published originally in Japanese that describe studies submitted in the Glaxo NDAs. The sponsor has previously submitted an NDA for a foam formulation of betamethasone valerate that was approved on February 28, 1999 (NDA 20-934).

Studies reviewed within this submission:
The sponsor has not conducted any preclinical studies with the clobetasol foam formulation. The foam vehicle was previously evaluated in several preclinical studies. These studies were reviewed in NDA 20-934 and ' for the betamethasone valerate foam product from Connetics.

PHARMACOLOGY:
Summary of pharmacology:
Clobetasol propionate acts, as do other glucocorticoids, through numerous mechanisms of action including inhibition of the arachidonic acid cascade, depression of cytokine production and effects on inflammatory cells. Topical products containing clobetasol propionate are generally among the most potent topical glucocorticoids as determined by vasoconstriction in the skin.

PHARMACOKINETICS/TOXICOKINETICS:
Summary:
Nonclinical studies in animals or in 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 pharmacokinetics of the sponsor's foam product was evaluated in the human clinical studies and the clinical and biopharmaceutics reviewers will review these data.

TOXICOLOGY:

General Comments:

As mentioned above, no toxicology studies have been conducted with the clobetasol propionate foam 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 studies clearly show that the topical application of clobetasol propionate can produce pronounced systemic exposures and effects. The established clinical use of corticosteroids has identified the following adverse effects as listed on the labels 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 labels of Temovate® or Cormax™ Scalp Application solutions, which are similar to the foam formulation, state that treatment beyond two weeks is not recommended.

Three animal studies were performed with the foam vehicle containing betamethasone valerate, 0.12%, to support NDA 20-934. The three studies were an acute dermal irritation study in rabbits, a skin sensitization study in guinea pigs and an acute eye irritation study in rabbits. Dr. Syed Alam reviewed these studies in [redacted]. The betamethasone foam was not a skin irritant in the rabbit or a sensitizer in the guinea pig. The foam was a moderate eye irritant in the rabbit.

From the results of the nonclinical and clinical studies conducted with topical clobetasol formulations and with the foam vehicle, there appears to be no reason to expect that the sponsor's formulation would lead to any previously uncharacterized toxicity.

CARCINOGENICITY:

Summary:

During the review of Connetics' NDA 20-934 for betamethasone valerate foam, it was discovered that the butane/propane propellant could possibly contain the probable human carcinogen [redacted] at a specification of 0.5 mole%. The sponsor subsequently was able lower this specification to 0.01 mole%. The sponsor also submitted a risk assessment for exposure to [redacted] from the propellant under exaggerated conditions of use. The results of this risk assessment showed that the specification of 0.01 mole % for dienes in the propellant appeared to ensure a level of [redacted] in the product that did not exceed a cancer risk of 1×10^{-6} except in extreme exposure scenarios.

Carcinogenicity studies on clobetasol have not been performed by the sponsor or by sponsors of previous NDAs for clobetasol.

REPRODUCTIVE TOXICOLOGY:
Summary and Evaluation:
Clobetasol, like other corticosteroids, is teratogenic in animals even when administered at relatively low doses. Reproductive toxicity studies specifically with clobetasol were conducted by Glaxo and by ? The results of these studies have been reviewed in the NDAs submitted by Glaxo for their clobetasol products. The sponsor has summarized the results of these studies.

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.

No preclinical teratogenicity studies have been conducted with topically applied clobetasol. However, systemic effects from topical clobetasol have been observed. Consequently, teratogenic effects from topical application of clobetasol can not be excluded.

Labeling Recommendations: The label should contain information about teratogenic and fetotoxic effects observed in the preclinical studies and the precautions and pregnancy category should be consistent with other topical clobetasol products.

GENETIC TOXICOLOGY:
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.

OVERALL SUMMARY AND EVALUATION:
Clobetasol propionate is available in several topical formulations and has been well studied in a variety of nonclinical studies. The current formulation is a foam, which is similar in composition to marketed solution formulations. Studies have been conducted with the foam vehicle and a betamethasone containing foam product. These studies suggest that the clobetasol propionate foam formulation should not produce any unexpected toxicity.

Conclusion:
The pharmacology and toxicology information is adequate to support approval of the new drug application for clobetasol propionate 0.05% foam.

Communication Review:

- Labeling Review (NDA):
  The first sentence in the **Carcinogenesis, Mutagenesis and Impairment of Fertility** section of the label states that "[redacted]." However, a segment I reproductive toxicity study in rats using subcutaneous administration of clobetasol propionate has been conducted and is included in the submission. The significant results of this study are described in the third paragraph of the **Carcinogenesis, Mutagenesis and Impairment of Fertility** section. Consequently, the first sentence of this section should be changed to read, "Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate."

  In the teratogenicity section of the label, Temovate products include two paragraphs with specific information about the subcutaneous teratogenicity studies conducted in mice and rabbits. This information is not included in the Olux label. This information is derived from unpublished studies conducted by Glaxo in support of their NDAs. This information should be included in the Olux label. The two paragraphs listed below include this information and compare dose multiples using a body surface area basis. The dose multiples in these two paragraphs differ from the ones presented in the Temovate labels. It is not clear how the animal to human dose multiples were calculated in the Temovate labels. Calculations based on either mg/kg or body surface area comparisons produce numbers that are different from those in the Temovate label. The calculations for the Olux dose multiple comparisons are included in the attached appendix.

  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, respectively, the human topical dose of Olux based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities.

  In rabbits, clobetasol propionate was teratogenic at doses of 0.003 and 0.01 mg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of Olux based on body surface area comparisons. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

Comments on Clinical studies section:
The table in the clinical studies section would be clearer if it included the total number of patients in each treatment group. The absolute number of subjects with each parameter clear at endpoint or achieving treatment success can not be meaningfully compared between groups without knowing the total number in each group. The reader must refer to the parenthetical percentages to obtain any meaningful information from this table. The table would be a clearer description of the study if the total number of subjects in each treatment group were included so that the reader could use the absolute numbers in each group for comparison, if so desired.

From the information presented in the table, it is not clear if there were 63 or 64 subjects in the Temovate Scalp Application treatment group.

Note: These comments on the clinical studies section of the label have been conveyed to the reviewing medical officer.

RECOMMENDATIONS:

Internal comments: The NDA is approvable from a pharm/tox perspective with minor labeling changes.

Labeling Recommendations: The sponsor should change the first sentence of the **Carcinogenesis, Mutagenesis and Impairment of Fertility** section of the label to state, "Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate." This recommendation is made since a fertility study has been conducted and is described in the label.

The two paragraphs as modified from the Temovate label describing the mouse and rabbit teratogenicity studies should be included in the label with Olux substituted for Temovate.

/S/ 12/7/99

Paul C. Brown, Ph.D.
Reviewing Pharmacologist

cc:
NDA 21-142
HFD-340
HFD-540
HFD-540/Pharm/Brown
HFD-540/TL/Jacobs
HFD-540/MO/Huene
HFD-540/Chem/Turujman
HFD-540/PM/Bhatt

Concurrence Only:
HFD-540/DD/Wilkin

HFD-540/TL/Jacobs a.g 12/7/99

Draft date (# of drafts): December 3, 1999 (1st draft)
December 7, 1999 (2nd draft)

12/29/99

Appendix/attachments: Appendix 1: Dose multiple calculations.

✓ DFS

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Appendix 1: Dose multiple calculations.

Maximum human dose:

$$\frac{50 \text{ g foam / week}}{7 \text{ days / week}} = 7.1 \text{ g foam / day}$$

$$7.1 \text{ g foam / day} \times 0.05\% = 3.6 \text{ mg clobetasol propionate / day}$$

$$\frac{3.6 \text{ mg / day}}{60 \text{ kg}} = 0.06 \text{ mg / kg / day} \quad \text{(assumes 60 kg human)}$$

$$0.06 \text{ mg / kg / day} \times 37 = 2.22 \text{ mg / m}^2 \text{ / day} \quad (km = 37)$$

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 ($mg/m^2 \div 2.22\ mg/m^2$)
Mouse (*km* = 3)		
1	3	1.4
.03	0.9	0.04
Rabbit (*km* = 12)		
0.003	0.036	0.02
0.01	0.120	0.05

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