

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-076

PHARMACOLOGY REVIEW(S)



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: 22-076
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: June 28, 2006
PRODUCT: Locoid (hydrocortisone butyrate) lotion, 0.1%
INTENDED CLINICAL POPULATION: Atopic dermatitis (≥ 3 months old)
SPONSOR: Ferndale Laboratories
DOCUMENTS REVIEWED: Nonclinical volumes 1 – 7 (Paper CTD NDA submission)
REVIEW DIVISION: Division of Dermatology and Dental Products (HFD-540)
PHARM/TOX REVIEWER: Barbara Hill, Ph.D.
PHARM/TOX SUPERVISOR: Paul Brown, Ph.D.
DIVISION DIRECTOR: Susan Walker, M.D.
PROJECT MANAGER: Melinda Bauerlien

Date of review submission to Division File System (DFS): 2-28-07

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability – The Locoid lotion, 0.1% NDA is approvable from a pharmacological/toxicological perspective.
- B. Recommendation for nonclinical studies – A dermal carcinogenicity study conducted with Locoid lotion, 0.1% is recommended as a Phase 4 commitment.
- C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the “Suggested Labeling” section located at the end of this review.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings – Hydrocortisone butyrate elicited the characteristic toxicities associated with a corticosteroid.
- B. Pharmacologic activity – Corticosteroid
- C. Nonclinical safety issues relevant to clinical use – None at this time

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-076
Review number: 1
Sequence number/date/type of submission: 000 / 7-20-06 / Original NDA submission
000 / 8-21-06 / BL
Information to sponsor: No
Sponsor and/or agent: Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale, MI 48220

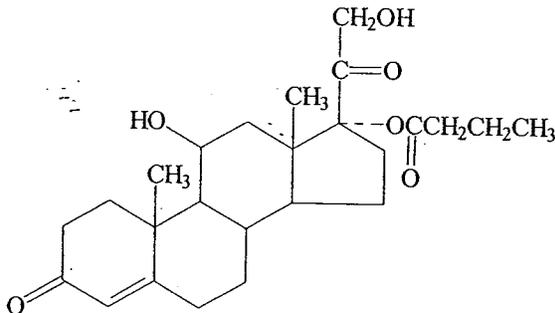
Manufacturer for drug substance: _____

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Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 1-22-07

Drug:

Trade name: Locoid lotion, 0.1%
Generic name: Hydrocortisone butyrate lotion, 0.1%
Code name: N/A
Chemical name: pregn-4-ene-3, 20-dione, 11, 21-dihydroxy-17-[(1-oxobutyl)oxy-,(11(beta))-
CAS registry number: 13609-67-1
Molecular formula/molecular weight: C₂₅H₃₆O₆ / 432.5
Structure:



Relevant INDs/NDAs/DMFs:

- 1) NDA 18-514 (Locoid {hydrocortisone butyrate} cream, 0.1%; Corticosteroid responsive dermatoses; HFD-540; approved 3/3/82)
- 2) NDA 18-652 (Locoid {hydrocortisone butyrate} ointment, 0.1%; Corticosteroid responsive dermatoses; HFD-540; approved 10/29/82)
- 3) NDA 19-116 (Locoid {hydrocortisone butyrate} solution, 0.1%; Seborrheic dermatitis; HFD-540; approved 2/25/87)
- 4) NDA 20-769 (Locoid {hydrocortisone butyrate} lipocream, 0.1%; Corticosteroid responsive dermatoses; HFD-540; approved 9/8/97)
- 5) IND 64,845 (Hydrocortisone butyrate lotion, 0.1%; atopic dermatitis; HFD-540)

Drug class: Corticosteroid, anti-inflammatory

Intended clinical population: Atopic dermatitis in adult and pediatric patients (≥3 months)

Clinical formulation:

The composition of the Locoid lotion, 0.1% is provided below.

Ingredient	% w/w
Hydrocortisone butyrate, USP	0.10
Butylated hydroxytoluene, NF	
Butylparaben, NF	
Ceteth-20	
Cetostearyl alcohol, NF	
Citric acid, USP, anhydrous	
Light mineral oil, NF	
White petrolatum, USP	
Propylparaben, NF	
Safflower oil, USP	
Sodium citrate dihydrate, USP	
Purified water, USP	

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The compositions of the four marketed locoid formulations are provided below for comparison purposes. The locoid cream and locoid lipocream formulations are closely related in composition to the proposed locoid lotion formulation.

LOCOID® Cream 0.1%

Each gram of LOCOID® cream contains 1 mg of hydrocortisone butyrate in a hydrophilic base consisting of cetostearyl alcohol, ceteth-20, mineral oil, white petrolatum, citric acid, sodium citrate, propylparaben and butylparaben (preservatives) and purified water.

LOCOID® Ointment 0.1%

Each gram of LOCOID® ointment contains 1 mg of hydrocortisone butyrate in a base consisting of mineral oil and polyethylene.

LOCOID® Solution 0.1%

Each mL of LOCOID® solution contains 1 mg of hydrocortisone butyrate in a vehicle consisting of isopropyl alcohol (50%), glycerin, povidone, citric acid, sodium citrate and purified water.

LOCOID Lipocream 0.1%

Each gram of LOCOID Lipocream® Cream contains 1 mg of hydrocortisone butyrate in a hydrophilic base consisting of cetostearyl alcohol, ceteth-20, mineral oil, white petrolatum, citric acid, sodium citrate, propylparaben and butylparaben (preservatives) and purified water.

Route of administration: Topical

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

Background:

Hydrocortisone butyrate is a synthetic, non-fluorinated, corticosteroid. Four topical dosage forms of hydrocortisone butyrate, 0.1% are currently being marketed under the trade name Locoid. The four topical preparations of hydrocortisone butyrate are a cream, lipocream, ointment and solution. The current 505(b)(1) NDA application provides information for a lotion dosage form of hydrocortisone butyrate, a line extension application. The sponsor for the new hydrocortisone butyrate topical formulation developed the four other hydrocortisone butyrate topical formulations that are currently on the market.

A guidance meeting was conducted with the sponsor on January 20, 2004. An End-of-Phase 2 meeting was conducted with the sponsor on March 29, 2004. A pre-NDA meeting was conducted with the sponsor on January 5, 2006. It was determined after review of the original IND submission that several Pharmacology/Toxicology data gaps existed for hydrocortisone butyrate. No genetic toxicology studies have been conducted with hydrocortisone butyrate. It was recommended that a full ICH battery of genetic toxicology be conducted with hydrocortisone butyrate. No fertility and reproductive developmental studies or perinatal and postnatal developmental studies have been conducted with hydrocortisone butyrate. It was recommended that these nonclinical studies be conducted with hydrocortisone butyrate to bring the label up to current standards. It was recommended that the final study reports for the recommended studies be included in the NDA submission. No carcinogenicity studies have been conducted for hydrocortisone butyrate. Treatment of corticosteroid responsive dermatoses is considered a chronic indication. Therefore, a dermal carcinogenicity study with Locoid lotion was recommended as a phase 4 commitment. In addition, it was recommended that the sponsor include a timeline for conduct of this study with the NDA submission.

The sponsor submitted final study reports for the genetic toxicology and reproductive and developmental toxicology studies conducted with hydrocortisone butyrate in this NDA submission. In addition, the sponsor has agreed to conduct a dermal carcinogenicity study with Locoid lotion as a phase 4 commitment and included a timeline for conduct of this study in the NDA submission. This sponsor submitted a paper CTD NDA submission for Locoid lotion. Per the Division's request, the sponsor submitted labeling for Locoid lotion in SPL format and in the new PLR format on August 21, 2006.

Studies reviewed within this submission:

Genetic toxicology

- 1) *In vivo* mouse micronucleus assay with hydrocortisone 17-butyrate (Study number 24414-0-455)

Reproductive and developmental toxicology

- 1) Fertility and early embryonic development to implantation in rats with hydrocortisone 17-butyrate (Study number 965-002)
- 2) Range-finding study for effects on embryo-fetal development in New Zealand white rabbits with hydrocortisone 17-butyrate (Study number 965-004)
- 3) Effects on embryo-fetal development in rats with hydrocortisone 17-butyrate (Study number 965-005)
- 4) Effects on embryo-fetal development in New Zealand white rabbits with hydrocortisone 17-butyrate (Study number 965-006)
- 5) Toxic effects on pre- and postnatal development including maternal function in rats with hydrocortisone 17-butyrate (Study number 965-007)

Studies not reviewed within this submission:

The final study reports for the studies listed below were included in the NDA submission, but were also previously submitted and reviewed under the IND. The IND serial number that these final study reports were submitted to is annotated for each study. A summary of the information from these studies is provided in this NDA review. The reader is referred to the reviews that have been entered into DFS of the appropriate IND serial number for additional detail, if needed.

Genetic toxicology (Submitted in Serial # 006)

- 1) *Salmonella-Escherichia coli*/Mammalian-microsome reverse mutation assay with hydrocortisone 17-butyrate (Study number 24414-0-409)
- 2) L5178Y TK[±] mouse lymphoma forward mutation assay with a confirmatory assay (Study number 24414-0-431)

Reproductive and developmental toxicology (Submitted in Serial # 006)

- 1) Range-finding study for effects on embryo-fetal development in rats with hydrocortisone 17-butyrate (Study number 965-003)

Special toxicology (Submitted in original IND submission)

- 1) Twenty-eight day acute dermal irritation/corrosion – OECD (Study number 02-0517-G1)

2.6.2 PHARMACOLOGY**2.6.2.1 Brief summary**

The following information concerning desonide pharmacological activity is contained in the proposed Locoid lotion label under the “CLINICAL PHARMACOLOGY; Mechanism of Action” section.

“Like other topical corticosteroids, hydrocortisone butyrate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.”

Reviewer's comment: The information contained in this section of the label appears to be relatively standard information that describes the mechanism of action for corticosteroids.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to brief summary

Drug activity related to proposed indication: Refer to brief summary

2.6.2.3 Secondary pharmacodynamics – N/A**2.6.2.4 Safety pharmacology**

No safety pharmacology studies have been conducted with hydrocortisone-butyrate. No safety pharmacology studies are recommended for hydrocortisone butyrate, at this time.

2.6.2.5 Pharmacodynamic drug interactions – N/A**2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A****2.6.4 PHARMACOKINETICS/TOXICOKINETICS****2.6.4.1 Brief summary**

The pharmacokinetics of hydrocortisone butyrate has been examined in dogs, rats and humans. Hydrocortisone butyrate is converted to hydrocortisone 21-butyrate and later to hydrocortisone. The majority of metabolism occurs in the liver by serum esterases. The serum half-life of hydrocortisone butyrate is 6 – 10 hours. Hydrocortisone is ~90% reversibly bound to two plasma proteins, corticosteroid-binding globulin (CBG) and albumin. CBG has a high binding affinity and low binding capacity for steroids while albumin has a low affinity but relatively large binding capacity for steroids.

Metabolism of hydrocortisone involves oxidation followed by conjugation to form water-soluble conjugates. Reduction of the 4,5 double bond in the A ring of hydrocortisone also occurs. This reduction can occur at both hepatic and extrahepatic sites to yield inactive compounds. The 3-ketone on the A ring can also be reduced to a hydroxyl group. This step only occurs in the liver. Conjugation (sulfate or glucuronide) of the reduced A ring steroids at the 3-hydroxyl group mostly occurs in the liver and, to a lesser extent, in the kidney. The sulfate esters and glucuronide conjugates are the predominant form excreted in the urine. Biliary and fecal excretion of steroids is relatively minor in humans.

In general, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

The following information concerning hydrocortisone butyrate pharmacokinetics activity is contained in the proposed Locoid lotion label under the "CLINICAL PHARMACOLOGY; Pharmacokinetics" section.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings or widespread application may increase the possibility of hypothalamic-pituitary-adrenal (HPA) axis suppression.

Locoid® is in the medium range of potency as compared with other marketed topical corticosteroids in vasoconstrictor studies.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids.

Corticosteroids are bound to plasma proteins in varying degrees.

Reviewer's comments: The information contained in this section of the label appears to be older standard information that describes the pharmacokinetics for corticosteroids. The Clinical Pharmacology and Biopharmaceutics reviewer will determine the adequacy of this information.

2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption – Refer to brief summary

2.6.4.4 Distribution – Refer to brief summary

2.6.4.5 Metabolism – Refer to brief summary

2.6.4.6 Excretion – Refer to brief summary

2.6.4.7 Pharmacokinetic drug interactions – N/A

2.6.4.8 Other Pharmacokinetic Studies – N/A

2.6.4.9 Discussion and Conclusions

Adequate pharmacokinetic information is available for hydrocortisone butyrate. No additional pharmacokinetic studies are recommended for Locoid lotion at this time.

2.6.4.10 Tables and figures to include comparative TK summary – N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY – N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The acute toxicology of hydrocortisone butyrate has been evaluated in mice and rats after oral, intraperitoneal or subcutaneous administration. The LD₅₀ values in male and female mice after intraperitoneal administration were 1550 and 1750 mg/kg, respectively. The LD₅₀ values in male and female mice after subcutaneous administration were 3000 and 2500 mg/kg,

respectively. The LD₅₀ values in male and female mice after oral administration was 3000 mg/kg. The LD₅₀ values were >3000 mg/kg in male and female rats after administration by all three routes.

Several nonclinical subchronic and chronic toxicity studies that ranged from 28 days to 7 months have been conducted with hydrocortisone butyrate after topical, subcutaneous and oral administration. Five of the seven repeat dose toxicity studies conducted with hydrocortisone butyrate were performed in rats (3 subcutaneous studies, 1 oral study and 1 topical study). One repeat dose toxicity study was conducted in dogs (30 day subcutaneous study) and the other repeat dose toxicity study was conducted in rabbits (6 month topical study).

Dose-dependent corticosteroid related findings were noted in all the repeat dose toxicity studies performed with hydrocortisone butyrate. The noted toxicity findings included:

- Decreased body weights
- Thymus, pancreas, spleen, skin and adrenal atrophy
- Increased number of infections
- Increased urea, triglyceride, potassium, calcium, glucose and alkaline phosphate levels
- Male animals were more sensitive to the toxic effects of hydrocortisone butyrate than female animals

The lowest dose administered in rats after topical (2 months), subcutaneous (3 months) and oral (28 days) exposure was 0.02, 0.003 and 1 mg/kg/day, respectively. A no-observable-effect-level (NOEL) was only determined after subcutaneous administration in rats. The subcutaneous NOEL in the 3 month repeat dose toxicity study conducted in rats was 0.03 mg/kg/day in male rats. A subcutaneous NOEL could not be determined in female rats in this study.

The sponsor has developed the Locoid lotion for treatment of a pediatric population (≥ 3 months of age). No nonclinical repeat dose dermal toxicology studies have been conducted with any topical formulation of hydrocortisone butyrate in juvenile animals. However, the effects of corticosteroids in pediatric patients have been well established for systemic and topical corticosteroids. Therefore, it was determined that it is not necessary for the sponsor to conduct nonclinical repeat dose dermal toxicology studies for Locoid lotion in juvenile animals.

In conclusion, no additional general toxicology studies are recommended for Locoid lotion at this time.

Genetic toxicology:

Hydrocortisone butyrate was evaluated for genotoxicity in a battery of in vitro and in vivo genetic toxicology studies. Hydrocortisone butyrate was negative in an in vitro bacterial mutagenesis assay (Ames test), an in vitro mammalian cell mutagenesis assay (L5178Y/TK⁺ mouse lymphoma assay) and an in vivo mouse micronucleus-assay.

The sponsor has conducted a full battery of genetic toxicology studies for hydrocortisone butyrate according to ICH guidelines. No additional genetic toxicology studies are recommended for Locoid lotion.

Carcinogenicity:

No carcinogenicity studies have been conducted for hydrocortisone butyrate. Treatment of corticosteroid responsive dermatoses is considered a chronic indication. Therefore, a dermal carcinogenicity study for Locoid lotion was recommended as a phase 4 commitment after review of the original IND submission. The sponsor agreed to conduct a dermal carcinogenicity study with Locoid lotion as a Phase 4 commitment in the NDA submission. The sponsor has provided the following timeline for conduct of the dermal carcinogenicity study with Locoid lotion.

Protocol Submission: _____ after date of NDA approval

Study Start: _____ after protocol approval

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Final Study Report Submission: _____ after study completion

The overall timeline proposed by the sponsor for the dermal carcinogenicity study and does not contain adequate detailed information. It is preferable to have actual dates in the timeline for tracking in the Post-marketing study database. The recommended timeline that incorporates dates for the various steps involved in the conduct of a dermal carcinogenicity study with the drug product as a phase 4 commitment is provided in the "Recommendations" section of this review.

The recommended timeline was based on the assumption that the approval date for Locoid lotion is May 20, 2007 (rounded up to June 1, 2007 for easier calculations). The date for submission of the 90-day dose range finding study report is 12 months after the approval date (June 1, 2008). The date for submission of the dermal carcinogenicity study protocol is 6 months after submission of the 90-day dose range finding study report (December 1, 2008). The date for starting the study is 9 months after submission of the study protocol (September 1, 2009). The date for submitting the final study report for the 2-year dermal carcinogenicity study is 3.5 years after the study start date (March 1, 2013).

The sponsor submitted information to address the photoco-carcinogenic potential of hydrocortisone butyrate in the original IND submission. A summary of the submitted information is provided below. It was determined that a study to determine the photoco-carcinogenic potential of hydrocortisone butyrate is not necessary. Therefore, a study to determine the photoco-carcinogenic potential of Locoid lotion is not recommended at this time.

A submitted published article¹ described a photoprotective effect in hairless mice of topical anti-inflammatory agents against chronic skin damage induced by UVB and UVA.

¹ Bissett DL, Chatterjee R, Hannon DP. Photoprotective effect of topical anti-inflammatory agents against ultraviolet radiation induced chronic skin damage in the hairless mouse. *Photodermatol. Photoimmunol. Photomed.* 7: 153-158, 1990.

Female albino hairless Skh:hr-1 mice (10/group; 10 weeks old) were treated with 0.1 ml of 0, 0.5%, 1%, or 2% hydrocortisone (2:1:1 (v:v:v) propylene glycol:ethanol:water vehicle) 2 hours prior to each irradiation. The 0.1 ml volume of treatment provided $\sim 2 \text{ mg/cm}^2$ coverage of the skin treatment site. Two other test articles were evaluated in this study (0.5%, 1% or 2% ibuprofen and 1% or 2% naproxen). The results from these test articles will not be described in this document.

Irradiation was conducted on a set of animals with UVB light (Westinghouse FS-40 sunlamps) 3X/week (Monday, Wednesday, Friday) with 30 mJ/cm^2 per exposure ($\sim 1/2$ the mouse MED). Another set of animals was irradiated with UVA light (GE F-40 black lights) 5X/week (Monday – Friday) with 15 J/cm^2 per exposure. Irradiation treatments with UVB or UVA light continued for 24 or 26 weeks, respectively. Skin wrinkling (UVB radiation), skin sagging (UVA radiation), skin tumors (UVB radiation), and histological evaluation (UVB or UVA radiation) of visibly non-tumor bearing dorsal skin were analyzed. The histological parameters evaluated in this study included epidermal thickness, glycosaminoglycan (GAG) content, dermal cellularity, elastosis, collagen damage, and dermal cyst changes.

Exposure to hydrocortisone followed by UVB reduced the severity of UVB effects. A dose-dependent increase in photoprotection (anti-wrinkling) with increasing concentration of test material was observed in this study. Body weights were significantly reduced (13% or 12%) in the animals treated with hydrocortisone compared to vehicle or untreated control animals, respectively. Time to tumor and number of tumors was delayed (22.2 weeks vs 19.1 weeks) or decreased (4 tumors vs 9 tumors at week 24) in animals treated with 1% hydrocortisone compared to the vehicle treated animals. Histological parameters (i.e., collagen, elastin, GAGs, epidermal thickness and dermal cellularity) analyzed at week 20 were also statistically significantly decreased in animals treated with 1% hydrocortisone followed by UVB compared to vehicle treated plus irradiation animals.

Hydrocortisone (0.5%) also reduced the severity of UVA effects in UVA irradiated animals. The onset of visible damage was delayed in animals treated with 0.5% hydrocortisone. Histological parameters (elastin, epidermal thickness and dermal cellularity) measured at week 26 were also reduced in animals treated with 0.5% hydrocortisone.

In summary, application of 0.5% or 1% hydrocortisone prior to UVB or UVA irradiation for 26 or 24 weeks reduced UVA and UVB-induced visible wrinkling, visible sagging, tumor formation and histological alterations.

Even though the sponsor has not addressed the photoco-carcinogenic potential of hydrocortisone butyrate, this published article suggests that hydrocortisone has photoprotective effects in hairless mice after UVA or UVB exposure. The protocol used for this study is quite different from the traditional photoco-carcinogenicity study in hairless mice. However, it was determined in the Pharmacology/Toxicology review for Locoid lipocream (NDA 20-729; conducted by Dr. Javier Avalos) that the findings in the literature article are encouraging and do not necessitate the re-evaluation of the potential enhancement of UV carcinogenesis. Therefore, it was determined that a study to determine the photoco-carcinogenic potential of hydrocortisone

butyrate is not necessary. Therefore, a study to determine the photoco-carcinogenic potential of Locoid lotion is not recommended at this time.

Reproductive toxicology:

Four embryofetal developmental toxicity studies were reviewed to support the locoid cream, 0.1% application (NDA 18-514). Hydrocortisone butyrate was administered topically to rabbits and rats or subcutaneously to rats and mice. The sponsor was informed after review of the original IND submission that no fertility and reproductive developmental studies or perinatal and postnatal developmental studies have been conducted with hydrocortisone butyrate. It was recommended that these nonclinical studies be conducted with hydrocortisone butyrate to bring the label up to current standards. It was recommended that the final study reports from these reproductive and developmental toxicology studies be included with the NDA submission. The sponsor was referred to the existing ICH guidelines (ICH-S5A, ICH-S5B, ICH-S5B(M)) available that discuss recommendations for conduct of reproductive and developmental toxicity studies.

Although only the fertility and peri- and post-natal developmental studies were recommended by the Agency, the sponsor conducted the full ICH battery of reproductive and developmental toxicology studies with subcutaneous hydrocortisone butyrate to support the new hydrocortisone butyrate lotion formulation.

Final study reports for a subcutaneous rat fertility study, a subcutaneous rat embryofetal development study, a subcutaneous rabbit embryofetal development study and a subcutaneous rat peri- and post-natal developmental study were included in the NDA submission. All of these studies were conducted with hydrocortisone butyrate according to current standards. These studies provide useful information for labeling purposes. It is recommended that the results of these studies be incorporated into the Locoid lotion label.

Summary of the reproductive toxicology studies conducted with hydrocortisone butyrate to support this NDA submission

Subcutaneous doses of 0 (vehicle: propylene glycol), 0.2 0.6 and 1.8 mg/kg/day hydrocortisone butyrate were administered in the rat fertility study. Subcutaneous doses were administered daily starting at 4 weeks prior to mating and during mating for males, and 14 days prior to mating and through gestation day 7 for females. A dose dependent decrease was noted in low, mid and high dose male and female bodyweight gain during the premating period compared to control animals. A treatment related decrease in bodyweight gain was noted in low, mid and high dose males during the mating period compared to control animals. A treatment related decrease in body weight was noted in low and high dose females during gestational days 0 - 7 compared to control animals. A NOAEL for paternal and maternal toxicity could not be established in this study based on decreased body weight gains noted in low, mid and high dose male and female animals compared to control animals. No treatment related effects on male or female fertility were noted in this study. A NOAEL for effects on fertility was identified as 1.8 mg/kg/day hydrocortisone butyrate in male and female rats, the highest dose tested in this study.

Subcutaneous doses of 0 (vehicle: propylene glycol), 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate were administered to pregnant rats (gestational days 6 – 17) in the rat embryofetal development study. A dose dependent decrease in body weight gain was noted in low, mid and high dose animals during gestational days 6 – 18 compared to control animals. A treatment related decrease in food consumption was noted in low, mid and high dose animals during gestational days 6 – 18 compared to control animals. A NOAEL for maternal toxicity could not be established in this study based on decreased body weight gains and food consumption noted in low, mid and high dose animals compared to control animals. An increased incidence of litters containing fetuses with ossification variations and an increased litter incidence of unossified sternebra in fetuses was noted in the high dose group compared to the control group. The NOAEL for teratogenicity was identified as 1.8 mg/kg/day hydrocortisone butyrate in male and female rats based on a delayed ossification signal.

Subcutaneous doses of 0 (vehicle: propylene glycol), 0.1, 0.2 and 0.3 mg/kg/day hydrocortisone butyrate were administered to pregnant rabbits (gestational days 7 – 20) in the rabbit embryofetal development study. No treatment related effects on mortality, body weights or food consumption were noted in this study. An increased incidence of abortion was noted in the high dose groups (6/16 litters) compared to control animals (0/23 litters). Therefore, the NOAEL for maternal toxicity is 0.2 mg/kg/day hydrocortisone butyrate in rabbits. A NOAEL for embryotoxicity or teratogenicity was not established in this study. A dose dependent decrease in fetal body weight was noted in low (males: ↓22.6%, females: ↓24.1%), mid (males: ↓27.1%, females: ↓33.9%) and high (males: ↓29.7%, females: ↓58.7%) dose groups compared to control animals. Delayed ossification was noted in low, mid and high dose groups. A reduction of litter size, number of viable fetuses per animal and increased postimplantation loss was noted in mid and high dose groups. An increased litter incidence of fetal malformations (primarily skeletal malformations) was noted in the mid and high dose groups. Therefore, the NOAEL for embryotoxicity and teratogenicity for hydrocortisone butyrate was less than 0.1 mg/kg/day in rabbits, the lowest dose tested in this study.

Subcutaneous doses of 0 (vehicle: propylene glycol), 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate were administered to pregnant rats (gestation day 6 – lactation day 20) in the rat peri- and post-natal development study. A dose dependent decrease in gestation body weight gain (gestation days 6 – 20) was noted in low, mid and high dose groups (↓14%, ↓17% and ↓24%, respectively) compared to control animals. Therefore a NOAEL for maternal toxicity could not be established in this study. A dose dependent decrease in F₁ pup weight was noted in mid and high dose groups compared to control animals. The subcutaneous NOAEL for neonatal toxicity was 0.6 mg/kg/day hydrocortisone butyrate administered from gestation day 6 – lactation day 20. No treatment related effects on reproductive performance and fertility were noted in this study. The subcutaneous NOAEL for reproductive performance and fertility was 5.4 mg/kg/day hydrocortisone butyrate administered from gestation day 6 – lactation day 20, the highest dose administered in this study. Treatment related effects on sexual maturation (i.e., delay in vaginal opening and acceleration of preputial separation) were noted in the high dose group. No other treatment related effects on the development of F₁ pups were noted in this study. The NOAEL for post-natal development was 1.8 mg/kg/day hydrocortisone butyrate administered from gestation day 6 – lactation day 20.

Summary of the previously conducted reproductive toxicology studies with hydrocortisone butyrate

Four embryofetal developmental toxicity studies were reviewed to support the locoid cream, 0.1% application (NDA 18-514). Hydrocortisone butyrate was administered topically to rabbits and rats or subcutaneously to rats and mice. Topical administration of 0, 0.1%, 1% or 10% hydrocortisone or hydrocortisone butyrate as an ointment (a gel of liquid paraffin with 50% polyethylene) to pregnant Wistar rats (gestational days 6 – 15) resulted in no teratogenic findings. Animals were necropsied on day 20. Deaths of the dams was noted in the high dose groups for both test articles. Fetal weights were decreased in the 1% treated group. No marked differences were noted between the hydrocortisone and hydrocortisone butyrate treatment groups. The same formulation and concentrations were applied on New Zealand rabbits (gestational days 6 – 18). Animals were sacrificed on day 25. Deaths were noted in the 1% and 10% treatment groups. A dose dependent increase in fetal resorptions was noted in this study. No teratogenic findings were noted in either rats or rabbits following topical administration of hydrocortisone or hydrocortisone butyrate.

Subcutaneous doses of 0, 0.2 and 1 mg/kg/day hydrocortisone butyrate (in suspension) were administered to pregnant mice (gestational days 7 – 13). Subcutaneous doses of 0, 0.1 and 9 mg/kg/day hydrocortisone butyrate were administered to pregnant rats (gestational days 9 – 15). A portion of the treated mice were sacrificed on day 18 and a portion of the treated rats were sacrificed on day 20. The remainder of treated animals were sacrificed after weaning. Rat offspring from the second group were sacrificed at weaning. Mice offspring from the second group were sacrificed on day 42. No mouse or rat deaths were reported in any treated group. Decreased maternal body weights were noted in high dose rats only. Increased fetal deaths and resorptions were noted in high dose rats. Rat fetuses demonstrated a treatment related increase in the number of ossifications in caudal vertebrae. No differences in ossifications in caudal vertebrae compared to vehicle group were noted in mice fetuses. However, mice fetuses demonstrated an increased number of cervical ribs (45.6%) and clubbed legs (1 case) in the high dose group. These findings were also noted in animals (rats and mice) treated subcutaneously with hydrocortisone 21-acetate (8.4 mg/kg/day).

It was determined during the review of Locoid lipocream (NDA 20-769; Javier Avalos) that although only a few teratogenic findings were observed in this studies, corticosteroids as a group are teratogenic when administered systemically at relatively low dose levels and when some corticosteroids are applied topically. Therefore, it was deemed that a pregnancy category C was appropriate for hydrocortisone butyrate. The Locoid lipocream formulation was the most recent topical Locoid formulation prior to the new Locoid lotion formulation that has been developed under the current NDA submission. It is recommended that Locoid lotion be labeled as a pregnancy category C drug product based on the results of the subcutaneous rat and rabbit embryofetal development studies conducted with hydrocortisone butyrate.

The following information is included in the Locoid lipocream label for the reproductive and developmental toxicity potential of hydrocortisone butyrate. Locoid lipocream is designated as Pregnancy Category C.

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

In teratogenicity studies, topical administration of 1% or 10% hydrocortisone butyrate in an ointment to pregnant Wistar rats (gestational days 6-15) or New Zealand white rabbits (gestational days 6-18) resulted in no teratogenic findings. However, a dose-dependent increase in fetal resorptions was reported in rabbits, and fetal resorptions were observed in rats treated with 10% hydrocortisone butyrate.

The doses given to rats are approximately 8 to 80 times the human topical dose based on a body surface area comparison (assuming 100% absorption). For rabbits, the doses given were approximately 0.2 and 2 times the human topical dose.

Increased resorptions were also noted in Wistar rats given subcutaneous administrations of hydrocortisone butyrate (9 mg/kg/day; 3 times the human topical dose) on gestational days 9 through 15. In CS mice given subcutaneous administrations of 1 mg/kg/day (0.2 times the human topical dose), an increased number of cervical ribs and one fetus with clubbed legs was reported.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

LOCOID Lipocream® (hydrocortisone butyrate 0.1%) Cream should not be used extensively on pregnant patients, in large amounts, or for longer than two weeks.

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk.

Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Special toxicology:

Locoid lotion was evaluated for its potential to produce dermal irritation or corrosion in a 28 day rabbit repeat dose study. A dose of 0.5 g of Locoid lotion or vehicle was applied to a gauze pad and then applied to either a designated intact or abraded skin shaved site on the trunk of a rabbit. The patch was held in place with semi-occlusive dressing. Test article and vehicle were applied twice daily (four hours apart) for 28 days. A minimal to moderate level of irritation was noted in rabbits early (up to day 6) in the repeat dose dermal irritation study for

both Locoid lotion and vehicle. The level of irritation decreased with time with repeat dose administration until no irritation was noted by the end of the 28 day treatment period in rabbits. A similar result was noted for the Locoid lipocream in a repeat dose dermal irritation study conducted in rabbits. It would appear that a tolerance develops to the dermal irritating potential of the Locoid lotion formulation after repeat dose administration.

The sponsor submitted UVB/UVA/VIS spectra _____ of Locoid lotion and the individual excipients contained in Locoid lotion in the NDA submission. In addition, the sponsor submitted UVB/UVA/VIS spectra _____ for Locoid cream, Locoid ultracream and Locoid ointment in the NDA submission for comparison purposes. A small absorption shoulder was noted at _____ which was attributed to the presence of parabens in the formulation, which are common excipients in many topical drug products. No significant absorption was noted in the _____ range for Locoid lotion from a Pharmacological/Toxicological perspective. Therefore, the need for a nonclinical photoirritation study is waived for Locoid lotion. The sponsor states in the NDA submission that conduct of a clinical photoallergy study with Locoid lotion was stopped after receiving the UVB/UVA/VIS spectra _____ for Locoid lotion. This appears to be appropriate based on the submitted UVB/UVA/VIS spectra _____ for Locoid lotion.

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No additional special toxicology studies are recommended for Locoid lotion at this time.

2.6.6.2 Single-dose toxicity

No nonclinical single-dose toxicity studies were included in this submission.

2.6.6.3 Repeat-dose toxicity

No nonclinical repeat-dose toxicity studies were included in this submission.

2.6.6.4 Genetic toxicology

Study title *In vivo* mouse micronucleus assay with hydrocortisone 17-butyrate

Key findings: Hydrocortisone butyrate was negative in the *in vivo* mouse micronucleus assay, under the conditions of this study.

Study no.: 24414-0-455
Volume #, and page #: Volume 1, Module 4, Section 4.2.3.3.2.1, page 66
Conducting laboratory: _____
Date of study initiation: 10-14-02
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Hydrocortisone-17-butyrate, Lot# 001437
Vehicle: 0.5% Carboxymethylcellulose

b(4)

Methods

- Strains/species/cell line: CD-1 mice; 8 weeks old; 30.3 – 35.5 g; 6/sex/dose/timepoint
- Doses used in definitive study: 0, 500, 1000 and 2000 mg/kg hydrocortisone butyrate administered on 3 consecutive days; intraperitoneal; dose volume: 20 ml/kg
- Basis of dose selection: Intraperitoneal doses of 500, 1000 and 2000 mg/kg hydrocortisone butyrate, were administered to mice (3/sex/dose) on 3 consecutive days in a dose range finding study. This dose range finding study indicated that a maximum dose of 2000 mg/kg was well tolerated. Therefore, doses of 500, 1000 and 2000 mg/kg were selected for the definitive study.
- Negative controls: 0.5% Carboxymethylcellulose, i.p.
- Positive controls: Cyclophosphamide (80 mg/kg); oral (gavage); vehicle: water; dose volume: 10 ml/kg
- Incubation and sampling times: Three daily intraperitoneal doses of hydrocortisone butyrate or a single oral dose of cyclophosphamide were administered to mice. Bone marrow for analysis of nucleated cells was obtained from treated mice 24 hours after last dose administration.

Stained bone marrow slides were scored for micronucleus and the PCE (polychromatic erythrocytes) to NCE (normal chromatic erythrocytes) cell ratio. The micronucleus frequency (expressed as percent micronucleated cells) was determined by analyzing the number of micronucleated PCEs from at least 2000 PCEs per animal. The PCE:NCE ratio was determined by scoring the number of PCEs and NCEs observed while scoring at least 500 erythrocytes per animal.

Results

Study validity:

A test article was considered to be positive if there was a statistically significant increase in micronucleated PCEs above concurrent vehicle control values for at least one dose level, and a statistically significant dose-related response.

Solvent control mutant frequencies fell within established ranges. Positive control results were appropriate. Dose range selected for the definitive study was appropriate according to ICH guidelines.

Study outcome:

Mortality was noted in the low (1/6), mid (1/6) and high (2/6) dose groups. Clinical signs of toxicity noted in high dose animals included hypoactivity, irregular respiration, squinted eyes and/or rough haircoat. Bone marrow toxicity was noted as decreased PCE:NCE ratio in the high dose group.

No significant increase in micronucleated PCEs was noted in hydrocortisone butyrate treated groups compared to the corresponding vehicle control in this study.

2.6.6.5 Carcinogenicity

No nonclinical carcinogenicity studies were included in this submission.

2.6.6.6 Reproductive and developmental toxicology**Fertility and early embryonic development**

Study title: Fertility and early embryonic development to implantation in rats with hydrocortisone 17-butyrate

Key study findings:

A dose dependent decrease was noted in low, mid and high dose male and female bodyweight gain during the pre-mating period compared to control animals. A treatment related decrease in bodyweight gain was noted in low, mid and high dose males during the mating period compared to control animals. A treatment related decrease in body weight was noted in low and high dose females during gestational days 0 – 7 compared to control animals. A NOAEL for paternal and maternal toxicity could not be established in this study based on decreased body weight gains noted in low, mid and high dose male and female animals compared to control animals. No treatment related effects on male or female fertility were noted in this study. A NOAEL for effects on fertility was identified as 1.8 mg/kg/day hydrocortisone butyrate in male and female rats, the highest dose tested in this study.

Study no.:	965-002
Volume #, and page #:	Volume 2, Module 4, Section 4.2.3.5.1.1, page 2
Conducting laboratory:	
Date of study initiation:	2-20-03
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, and % purity:	Hydrocortisone butyrate, Lot# 01J24/95, 96.7%
Vehicle:	Propylene glycol

b(4)**Methods**

Doses: 0, 0.2, 0.6 and 1.8 mg/kg/day

(Doses selected for the rat fertility study were based on results noted in a subcutaneous rat range finding embryofetal development study conducted with 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate. A treatment related decrease in body weight gain was noted in mid and high dose animals compared to control animals. This study was reviewed under IND 64,845, Serial# 066.)

Species/strain:	Sprague-Dawley rats; 8 weeks; males: 222 – 260 g; females: 167 – 197 g
Number/sex/group:	25/sex/dose
Route, formulation, volume, and infusion rate:	Subcutaneous, Propylene glycol, 1 ml/kg
Satellite groups used for toxicokinetics:	N/A
Study design:	

Subcutaneous doses were administered daily starting at 4 weeks prior to mating and during mating for males, and 14 days prior to mating and through gestation day 7 for females. Females were mated on a one to one basis with the correspondingly treated 4 week dosed males. Females showing a sperm positive vaginal smear were separated from the males and remained isolated until sacrifice on gestation day 13. Males were sacrificed after the mating period.

Parameters and endpoints evaluated:

Toxicity parameters evaluated in this study included mortality (daily), clinical signs (daily), body weight (males: twice weekly during mating period; females: twice weekly during the mating period and on gestation days 0, 4, 7, 10 and 13), and food consumption (males: weekly during mating period; females: weekly during mating period and on gestation days 0, 4, 7, 10 and 13). Females were evaluated for estrous cyclicity 14 days prior to mating and until evidence of copulation was noted. Males were sacrificed for necropsy evaluation after completion of the mating period. A complete necropsy was performed in males and epididymids, prostate, seminal vesicles and testes organ weights were obtained. An analysis (concentration, motility, morphology) of the sperm was performed using the right testis and epididymis. The left testis and epididymis, prostate, and seminal vesicle were preserved for possible histopathological evaluation. Females were sacrificed for necropsy evaluation on gestation day 13. Organ weights for uterus and ovaries were obtained for all females. The following parameters were measured during the gross necropsy in females: the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. Ovaries, uterus and vagina were preserved for possible histopathological evaluation. The following fertility indices were evaluated in this study: Copulatory interval, male and female fertility index, male and female mating index, male and female fecundity index and estrous cyclicity (mean cycle time and # cycles/period).

Results

Mortality: No treatment related effects on mortality were noted in this study.

Clinical signs: No treatment related effects on clinical signs were noted in this study.

Body weight: A dose dependent decrease in body weight gain was noted in low, mid and high dose males (\downarrow 18.1%, \downarrow 26.4%, \downarrow 40.1%, respectively) during the pre-mating period (Days 1 – 29) compared to control males. A treatment related decrease in body weight gain was noted in low, mid and high dose males (\downarrow 13.2%, \downarrow 12.9%, \downarrow 20.4%, respectively) during the mating period (Days 29 - 50) compared to control males.

A dose dependent decrease in body weight gain was noted in low, mid and high dose females (\downarrow 9.2%, \downarrow 20.7%, \downarrow 32.3%, respectively) during the pre-mating period (Days 1 – 15) compared to control females. A treatment related decrease in body weight gain was noted in low and high dose females (\downarrow 11.3%, \downarrow 22.3%, respectively) during gestational days 0 – 7 compared to control females. No treatment related effects on body weight gain was noted in mid dose females during gestational days 0 – 7 compared to control females. No treatment related effects on body weight gain was noted during gestational days 7 – 13.

Food consumption: No treatment related decrease in food consumption was noted in low, mid and high dose males during the pre-mating and mating period compared to control males. No treatment related effects on food consumption was noted in female animals during the pre-mating period. A treatment related decrease in food consumption was noted in high dose females during gestational days 7 – 13 compared to control females.

Toxicokinetics: N/A

Necropsy: No treatment related effects on macroscopic parameters were noted in this study. No treatment related effects on organ weights were noted in this study.

Fertility parameters:

No treatment related effect on estrous cyclicity was noted in this study. No treatment related effects on reproductive indices (mating indices, fertility indices and fecundity indices) were noted in this study. No treatment related effects on copulatory interval was noted in this study.

A total of 24 pregnancies were noted in control, low and mid dose groups and 22 pregnancies were noted in the high dose group. No treatment related effects on uterine implantation data were noted in this study. The mean number of corpora lutea, uterine implantations, viable embryos, resorptions, pre-implantation loss and post-implantation loss for the low, mid and high dose groups were comparable to the control group.

No treatment related effects on sperm evaluations were noted in this study. Sperm motility, total caudal epididymal sperm concentrations, sperm concentrations per gram tissue and percent abnormal sperm in low, mid and high dose groups were comparable to the control group.

Embryofetal development

Study #1

Study title: Effects on embryo-fetal development in rats with hydrocortisone 17-butyrate

Key study findings:

A dose dependent decrease in body weight gain was noted in low, mid and high dose animals during gestational days 6 – 18 compared to control animals. A treatment related decrease in food consumption was noted in low, mid and high dose animals during gestational days 6 – 18 compared to control animals. A NOAEL for maternal toxicity could not be established in this study based on decreased body weight gains and food consumption noted in low, mid and high dose animals compared to control animals.

An increased incidence of litters containing fetuses with ossification variations and an increased litter incidence of unossified sternebra in fetuses was noted in the high dose group compared to the control group. The NOAEL for teratogenicity was identified as 1.8 mg/kg/day hydrocortisone butyrate in male and female rats based on a delayed ossification signal.

Study no.:	965-005	
Volume #, and page #:	Volume 4, Module 4, Section 4.2.3.5.2.3, page 2	b(4)
Conducting laboratory:		
Date of study initiation:	5-9-03	
GLP compliance:	Yes	
QA report:	Yes	
Drug, lot #, and % purity:	Hydrocortisone butyrate, Lot# 01J24/95, 96.7%	
Vehicle:	Propylene glycol	

Methods

Doses: 0, 0.6, 1.8 and 5.4 mg/kg/day
 (Doses selected for the definitive rat embryofetal development study were based on results noted in a subcutaneous rat range finding embryofetal development study conducted with 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate. A treatment related decrease in body weight gain was noted in mid and high dose animals compared to control animals. This study was reviewed under IND 64,845, Serial# 066.)

Species/strain:	female Sprague-Dawley rats (pregnant); 175 – 241 g
Number/sex/group:	25 females/group
Route, formulation, volume, and infusion rate:	Subcutaneous, Propylene glycol, 1 ml/kg
Satellite groups used for toxicokinetics:	N/A
Study design:	Subcutaneous doses were administered daily from gestation days 6 – 17

Parameters and endpoints evaluated:

Toxicity parameters evaluated in this study included mortality (daily), clinical signs (daily), maternal body weights (days 0, 6, 9, 12, 15, 18 and 20 of gestation) and food consumption (days 0, 6, 9, 12, 15, 18 and 20 of gestation). All maternal animals were sacrificed on gestation day 20. The maternal gross necropsy performed after sacrifice on gestational day 20 consisted of examination of the thoracic and abdominal cavities.

The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. All fetuses were weighed and examined for external findings and sex determination. Half of the fetuses were examined for soft tissue abnormalities and half of the fetuses were examined for skeletal abnormalities.

Results

Mortality (does): No treatment related effects on mortality were noted in this study.

Clinical signs (does): No treatment related effects on clinical signs were noted in this study.

Body weight (does): A dose dependent decrease in body weight gain was noted in low, mid and high dose females (\downarrow 11.3%, \downarrow 20.4%, \downarrow 24.1%, respectively) during the gestational days 6 – 18 compared to control females.

Food consumption (does): A treatment related decrease in food consumption was noted in low, mid and high dose females (\downarrow 9.6%, \downarrow 9.4%, \downarrow 6.0%, respectively) during the gestational days 6 – 18 compared to control females.

Toxicokinetics: N/A

Terminal and necroscopic evaluations:

No treatment related effects on maternal macroscopic parameters were noted in this study. Pregnancy rates in control and treated groups ranged from 96 – 100% and provided 23, 24, 24, and 25 litters for evaluation in the control, low, mid and high dose groups, respectively. No treatment related effects on uterine implantation data was noted in this study. The mean number of corpora lutea, uterine implantations, resorptions, pre- and post-implantation loss and viable fetuses per dam for the low, mid and high dose groups were comparable to the control group. No treatment related effect on gravid uterine weights was noted in this study. No treatment related effect on fetal body weight or fetal sex ratio was noted in this study.

Offspring:

No treatment related effects on external malformations were noted in this study. No treatment related soft tissue alterations, variations or malformations were noted in this study.

Evidence of delayed ossification was noted in high dose females. An increased incidence of litters containing fetuses with ossification variations was noted in high dose females compared to control females (84% vs 69.0%, respectively). A statistically significant increase in the litter incidence of unossified sternebrae was noted in high dose females compared to control females (56.0% vs 21.7%, respectively).

Study #2

Study title: Range-finding study for effects on embryo-fetal development in New Zealand White rabbits with hydrocortisone 17-butyrate

Study no.: 965-004

Volume #, and page #: Volume 4, Module 4, Section 4.2.3.5.2.2, page 146

Conducting laboratory:

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Subcutaneous doses of 0 (vehicle: propylene glycol), 0.2, 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate (dose volume: 1 ml/kg) were administered to pregnant New Zealand White rabbits (6/dose) during gestational days 7 – 20. Pregnancy rate was not affected in this study. One low dose female aborted on gestation day 21 and two mid-low dose females aborted on gestation days 22 and 21, respectively. An increased incidence of red material in the pan or red discharge from the vulva was noted in mid-low, mid-high and high dose females compared to control animals. No treatment related effect on body weight gain was noted in low dose females compared to control females. Maternal body weight gain was not calculated in mid-low, mid-high and high dose groups since all does in these dose groups completely resorbed the fetuses. Postimplantation loss was 100% in mid-low, mid-high and high dose groups. No treatment related effects on uterine implantation data was noted in the low dose group compared to control animals. The gravid uterine weight in the low dose group was significantly decreased by 28% compared to control animals which suggested fetal body weight reduction. The study report states that it can be concluded that a dose of 0.3 mg/kg/day will be chosen as the highest dose for the definitive rabbit embryofetal development study based on the toxicities noted in this study. *(This study is not reviewed in greater detail since this was a dose-ranging study and the definitive study is reviewed below.)*

Study #3

Study title: Effects on embryo-fetal development in New Zealand White rabbits with hydrocortisone 17-butyrate

Key study findings:

No treatment related effects on mortality, body weights or food consumption were noted in this study. An increased incidence of abortion was noted in the high dose groups (6/16 litters) compared to control animals (0/23 litters). Therefore, the NOAEL for maternal toxicity is 0.2 mg/kg/day hydrocortisone butyrate in rabbits.

A NOAEL for embryotoxicity or teratogenicity was not established in this study. A dose dependent decrease in fetal body weight was noted in low (males: ↓22.6%, females: ↓24.1%),

mid (males: ↓27.1%, females: ↓33.9%) and high (males: ↓29.7%, females: ↓58.7%) dose groups compared to control animals. Delayed ossification was noted in low, mid and high dose groups. A reduction of litter size, number of viable fetuses per animal and increased postimplantation loss was noted in mid and high dose groups. An increased litter incidence of fetal malformations (primarily skeletal malformations) was noted in the mid and high dose groups. Therefore, the NOAEL for embryotoxicity and teratogenicity for hydrocortisone butyrate was less than 0.1 mg/kg/day in rabbits, the lowest dose tested in this study.

Study no.: 965-006
Volume #, and page #: Volume 5, Module 4, Section 4.2.3.5.2.4, page 2
Conducting laboratory: _____
Date of study initiation: 4-25-03
GLP compliance: Yes
QA report: Yes
Drug, lot #, and % purity: Hydrocortisone butyrate, Lot# 01J24/95, 96.7%
Vehicle: Propylene glycol

b(4)

Methods

Doses: 0, 0.1, 0.2 and 0.3 mg/kg/day
 (Doses selected for the rabbit teratology study were based on results noted in a subcutaneous rabbit range finding embryofetal development study conducted with 0.2, 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate. The results of this study were described previously.)
 Species/strain: female New Zealand White rabbits (pregnant); 2.95 – 4.14 kg
 Number/sex/group: 23 females/group
 Route, formulation, volume, and infusion rate: Subcutaneous, Propylene glycol, 1 ml/kg
 Satellite groups used for toxicokinetics: N/A
 Study design: Subcutaneous doses were administered daily from gestation days 7 – 20

Parameters and endpoints evaluated:

Toxicity parameters evaluated in this study included mortality (daily), clinical signs (daily), maternal body weights (days 0, 7, 10, 13, 16, 18, 21, 25 and 29 of gestation) and food consumption (days 0, 7, 10, 13, 16, 18, 21, 25 and 29 of gestation). All maternal animals were sacrificed on gestation day 29. The maternal gross necropsy performed after sacrifice on gestational day 29 consisted of examination of the thoracic and abdominal cavities.

The following parameters were measured during the gross necropsy in pregnant females: gravid uterine weight, the number of early/late resorptions, live and dead fetuses, number and distribution of implantation sites and number of corpora lutea. All fetuses were weighed and examined for external findings and sex determination. All fetuses were examined for soft tissue and skeletal abnormalities.

Results

Mortality (does): No treatment related effects on mortality were noted in this study.

Clinical signs (does): An increased incidence of abortion was noted in the high dose groups (6/16 litters) compared to control animals (0/23 litters).

Body weight (does): No treatment related effects on maternal body weight were noted in this study.

Food consumption (does): No treatment related effects on food consumption were noted in this study.

Toxicokinetics: N/A

Terminal and necroscopic evaluations:

No treatment related effects on maternal macroscopic parameters were noted in this study. Pregnancy rates in control and treated groups ranged from 91.3 – 100% and provided 23, 22, 19, and 16 litters for evaluation in the control, low, mid and high dose groups, respectively. No aborted pregnancies were noted in control and low dose groups. One animal aborted in the mid dose group and six animals aborted in the high dose group.

A treatment related effect on uterine implantation data was noted in the mid and high dose groups compared to the control group. Smaller litter sizes and increased postimplantation loss was noted in the mid and high dose groups. The mean number of viable fetuses and litter size per dam was decreased in the mid and high dose groups. The mean number of resorptions (early plus late), late resorptions, and post implantation loss was higher in the mid and high dose groups but these differences were only statistically significant in the high dose group compared to the control group. The mean number of corpora lutea, uterine implantations, resorptions, pre- and post-implantation loss and viable fetuses per dam for the low dose groups were comparable to the control group. Gravid uterine weights were statistically decreased in low, mid and high dose groups (↓23.5%, ↓31.3%, ↓32.5%, respectively) compared to control. This was attributed to lower fetal body weights and a fewer number of viable fetuses *in utero*. A dose dependent decrease in fetal body weight was noted in low (males: ↓22.6%, females: ↓24.1%), mid (males: ↓27.1%, females: ↓33.9%) and high (males: ↓29.7%, females: ↓58.7%) dose groups compared to control animals. No treatment related effect on fetal sex ratio was noted in this study.

Offspring:

A treatment related external malformation (cleft palate) was noted in two high dose fetuses (one fetus from each of two litters). Treatment related skeletal malformations were noted in the mid and high dose groups. The incidences of litters containing at least one fetus with a skeletal malformation was 36.8% (7/19) and 56.3% (9/16) in the mid and high dose groups, respectively, which was statistically significantly greater the control group incidence of skeletal malformations (4.3%; 1/23). A high litter incidence of fused sternbrae was noted in the mid (15.8%; 3/19) and high dose groups (37.5%; 6/16) compared to control animals (4.3%, 1/23). A high litter incidence of absence of the interparietal skull bone was noted in the mid (21.1%; 4/19)

and high dose groups (6.3%; 1/16) compared to control animals (0%, 0/23). No treatment related effects on skeletal malformations were noted in the low dose group.

Delayed ossification was noted in low, mid and high dose groups. Ossification variations suggested of delayed ossification noted with increased frequency in the mid and high dose groups included: talus not ossified, pubis not ossified, reduction in number of full unilateral ribs, bent hyoid arch, hyoid body not ossified, incompletely ossified and/or misshapen interparietal, misshapen supraoccipital and ossified sternbrae. Ossification variations suggested of delayed ossification noted with increased frequency in the low dose group included: reduction in number of full unilateral ribs, bent hyoid arch, misshapen interparietal and/or supraoccipital bones and unossified sternbrae.

The incidences of litters containing at least one malformed fetus in the control, low, mid and high dose groups were 4.3%, 4.5%, 36.8% and 62.5%, respectively. The increase in malformations noted in the mid and high dose groups was primarily attributable to an increase in skeletal malformation, in particular, fused sternbrae and absence of the interparietal skull bone.

Prenatal and postnatal development

Study title: Toxic effects on pre- and postnatal development including maternal function in rats with hydrocortisone 17-butyrate

Key study findings:

A dose dependent decrease in gestation body weight gain (gestation days 6 – 20) was noted in low, mid and high dose groups (↓14%, ↓17% and ↓24%, respectively) compared to control animals. Therefore a NOAEL for maternal toxicity could not be established in this study. A dose dependent decrease in F₁ pup weight was noted in mid and high dose groups compared to control animals. The subcutaneous NOAEL for neonatal toxicity was 0.6 mg/kg/day hydrocortisone butyrate administered from gestation day 6 – lactation day 20. No treatment related effects on reproductive performance and fertility were noted in this study. The subcutaneous NOAEL for reproductive performance and fertility was 5.4 mg/kg/day hydrocortisone butyrate administered from gestation day 6 – lactation day 20, the highest dose administered in this study. Treatment related effects on sexual maturation (i.e., delay in vaginal opening and acceleration of preputial separation were noted in the high dose group). No other treatment related effects on the development of F₁ pups were noted in this study. The NOAEL for post-natal development was 1.8 mg/kg/day hydrocortisone butyrate administered from gestation day 6 – lactation day 20.

Study no.:	965-007	
Volume #, and page #:	Volume 6, Module 4, Section 4.2.3.5.3.1, page 2	b(4)
Conducting laboratory:		
Date of study initiation:	3-18-04	
GLP compliance:	Yes	
QA report:	Yes	

Drug, lot #, and % purity: Hydrocortisone butyrate, Lot# 01J24/95, 96.7%
Vehicle: Propylene glycol

Methods

Doses: 0, 0.6, 1.8 and 5.4 mg/kg/day
(Doses selected for the rat peri- and post-natal development study were based on results noted in a subcutaneous rat range finding embryofetal development study conducted with 0.6, 1.8 and 5.4 mg/kg/day hydrocortisone butyrate. A treatment related decrease in body weight gain was noted in mid and high dose animals compared to control animals. This study was reviewed under IND 64,845, Serial# 066.)

Species/strain: pregnant female Sprague-Dawley rats;
190 – 242 g
Number/sex/group: 25 females/dose
Route, formulation, volume, and infusion rate: Subcutaneous, Propylene glycol, 1 ml/kg
Satellite groups used for toxicokinetics: N/A
Study design: Subcutaneous doses were administered daily from gestation day 6 – lactation day 20

Parameters and endpoints evaluated:

F₀ female toxicity parameters evaluated in this study included mortality (daily), clinical signs (daily), body weight (days 0, 6, 10, 14, 17 and 20 of gestation and days 0, 4, 7, 10, 14, 17 and 21 of lactation), and food consumption (days 0, 6, 10, 14, 17 and 20 of gestation and days 0, 4, 7, 10, 14, 17 and 21 of lactation). Females were sacrificed for necropsy evaluation on lactation day 21.

F₁ pups were examined after birth for litter size, number of stillborn and liveborn pups, number of males and females, individual body weights and gross abnormalities. F₁ pups were culled to a litter size of 4 males and 4 females, where possible, on lactation day 4. F₁ pups toxicity parameters included mortality (daily), clinical signs (daily), body weight (days 0, 4, 7, 14 and 21 of lactation).

The behavioral and developmental indices were evaluated in F₁ pups: static righting reflex (lactation day 2), pinna detachment (lactation day 2), cliff aversion (lactation day 11), eye opening (lactation day 13), air drop righting reflex (lactation day 16), neuropharmacological evaluation (Irwin test on lactation day 21), auditory response (Preyer's test on lactation day 21), vaginal opening (evaluated in female pups beginning on day 28 of age), preputial separation (evaluated in male pups beginning on day 35 of age), motor activity (evaluated in an activity chamber on day 35 of age), step-through passive avoidance test (initiated between 74 to 75 days of age).

The reproductive potential was evaluated at 80 days of age, in one male and one female from each litter which were not used in the behavior test. Males and females from the same dose group were mated on a 1:1 basis for 2 weeks. F₁ females were weighed every 4 days during the gestation period. Mortality and clinical observations were measured daily during the copulation

period in F₁ males and females. Body weights were determined weekly in F₁ males until termination on gestation day 13. A gross necropsy was performed on euthanized F₁ males. Body weights were determined weekly in F₁ females during the copulation period and on gestation days 0, 7, 10 and 13. F₁ females were sacrificed on gestation day 13 for necropsy examination. The number of corpora lutea, implantation sites, dead or resorbed fetuses and live fetuses were determined for each F₁ female.

Results

F₀ in-life: No treatment related effects on mortality, clinical signs or food consumption were noted in F₀ maternal rats. A dose dependent decrease in gestation body weight gain (gestation days 6 – 20) was noted in low, mid and high dose groups (↓14%, ↓17% and ↓24%, respectively) compared to control animals. This decrease in gestation body weight gain correlated with decreased F₁ pup weight described below. No treatment related effect on lactation body weight gain was noted in this study. No treatment related effects on abortion or premature or abnormal delivery were noted in this study. The pregnancy rate was 100% in control, low and mid dose groups and 96% in the high dose group. There were 25, 23, 25 and 24 litters with live pups for evaluation in the control, low, mid and high dose groups, respectively. No treatment related difference in mean gestation length in the low, mid and high dose groups (range 21.8 – 21.9 days) compared to control group (22 days) was noted in this study.

F₀ necropsy: No treatment related effects on macroscopic findings were noted in F₀ maternal rats. No treatment related effect on F₁ pup survival or sex ratio were noted in this study.

F₁ physical development: A dose dependent decrease in F₁ pup weight was noted in mid and high dose groups compared to control animals. Combined male and female F₁ pup weight was decreased on days 0 (mid: ↓4.5%; high: ↓8.0%), 4 (mid: ↓3.3%; high: ↓7.1%) and 7 (mid: ↓6.5%; high: ↓9.2%) after birth compared to control animals. Combined male and female F₁ pup weight was comparable to control animals on days 14, 21 and 28 after birth.

No treatment related differences were noted for preweaning reflex tests (static righting and air-drop righting reflexes), developmental landmarks (pinna detachment and eye opening) or sensory responses (auditory startle and cliff aversion) in this study. A statistically significant delay in the vaginal opening was noted in high dose female F₁ pups (32.6 days) compared to control female F₁ pups (31.7 days). A statistically significant decrease in the preputial separation date was noted in high dose male F₁ pups (44.0 days) control male F₁ pups (45.8 days).

F₁ behavioral evaluation: No treatment related effects on the neuropharmacological evaluations, motor activity, or learning and memory evaluations (passive avoidance test) were noted in this study.

F₁ reproduction: No treatment related effects on the evaluated reproductive parameters were noted in F₁ pups.

F₂ findings: Not evaluated.

2.6.6.7 Local tolerance

No nonclinical local tolerance studies were included in this submission.

2.6.6.8 Special toxicology studies

No nonclinical special toxicology studies were included in this submission.

2.6.6.9 Discussion and Conclusions

An ICH battery of genotoxicity studies and an ICH battery of reproductive toxicology studies have been conducted with hydrocortisone butyrate. It is recommended that the results from these studies be incorporated into the Locoid lotion label. A nonclinical dermal carcinogenicity study has not been conducted with any topical hydrocortisone butyrate formulation. It had been previously determined that a study to determine the photoco-carcinogenic potential of hydrocortisone butyrate was not necessary. Therefore, the need for a study to determine the photoco-carcinogenic potential of Locoid lotion was waived. It was recommended that the sponsor conduct a dermal carcinogenicity study as a Post-marketing commitment. The sponsor has agreed to conduct a dermal carcinogenicity study with Locoid lotion as a Post-marketing commitment.

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

Refer to summaries provided above.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Based on the nonclinical data available for hydrocortisone butyrate, NDA 22-076 for Locoid lotion is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the Locoid lotion label.

The sponsor has agreed to conduct a dermal carcinogenicity study with Locoid lotion. The recommended timeline for conduct of this nonclinical study is provided in the "Recommendations" section below.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 22-076, at this time.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the Locoid lotion label.

It is recommended that the following nonclinical Post-marketing commitment information be included in an approval letter for Locoid lotion, if the drug product is approved from the perspective of the other reviewing disciplines.

1. The applicant commits to conducting a 2-year dermal carcinogenicity study with Locoid (hydrocortisone butyrate) lotion.

90-day dose range-finding study:

By June 1, 2008

Study protocol submission:

By December 1, 2008

Study start date:

By September 1, 2009

Final report submission:

By March 1, 2013

Suggested labeling:

For reference purposes, the dose ratio values (multiples of human exposure) based on body surface area comparisons (assuming 100% systemic absorption) between various species and man following exposure to Locoid lotion, 0.1% are provided in the following table. It was presumed that the maximum daily dose of Locoid lotion, 0.1% is 25 g/day for these calculations.

Species/Sex	Route	Dose (mg/kg/day)	Km factor	Dose (mg/m ²)	Dose ratio
Fertility study					
Rat	sc	0.2	6	1.2	0.08
		0.6	6	3.6	0.23
		1.8	6	10.8	0.69
Embryofetal development studies conducted under NDA 22-076					
Rat	sc	0.6	6	3.6	0.23
		1.8	6	10.8	0.69
		5.4	6	32.4	2.1
Rabbit	sc	0.1	12	1.2	0.08
		0.2	12	2.4	0.15
		0.3	12	3.6	0.23
Embryofetal development studies conducted under NDA 18-514					
Rat	sc	0.1	6	0.6	0.04
		9	6	54	3.5
Mouse	sc	0.2	3	0.6	0.04
		1	3	3	0.19
Peri- and Postnatal development study					
Rat	sc	0.6	6	3.6	0.23
		1.8	6	10.8	0.69
		5.4	6	32.4	2.1
Human	Topical	0.42 ^a	37	15.5	--

a – assuming a 60 kg individual with a maximum daily dose of 25 g/day Locoid lotion, 0.1% and assuming 100% systemic absorption (25 g Locoid lotion/day x 1 mg hydrocortisone butyrate/gm Locoid lotion + 60 kg = 0.42 mg/kg/day hydrocortisone butyrate)

In summary, the multiples of human exposure for all of the reproductive toxicology studies conducted with hydrocortisone butyrate that will be incorporated into the label range for 0.04 – 3.5.

The sponsor included a label for Locoid lotion in the new PLR format in the NDA submission. The nonclinical portions of the Locoid lotion label are provided below. It is recommended that the underlined highlighted wording be inserted into and the ~~strikeout~~ wording be deleted from the “Pregnancy” and “Carcinogenicity, Mutagenesis, Impairment of Fertility” sections of the Locoid lotion label.

3 Page(s) Withheld

 Trade Secret / Confidential (b4)

 x Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

cc:

DDDP/DIV DIR/WALKER
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO/KATZ
DDDP/PM/BAUERLIEN

APPENDIX/ATTACHMENTS

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Barbara Hill
3/12/2007 09:19:46 AM
PHARMACOLOGIST

Paul Brown
3/12/2007 01:27:17 PM
PHARMACOLOGIST