CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-802

PHARMACOLOGY REVIEW

Pharmacology/Toxicology Review

NDA 50-802

Drug: Clindamycin, 1%; tretinoin, 0.025%
Drug name: ZIANA Gel
Reviewer: Jill C. Merrill

Introduction:
This NDA was originally submitted as NDA 21-739 on February 6, 2004. On November 11, 2004 the NDA number was changed to NDA 50-802. Based on the nonclinical data available for clindamycin phosphate and tretinoin, NDA 50-802 was approvable from a pharmacological/toxicological perspective, with no additional nonclinical studies recommended. However, the NDA was considered non-approvable based on CMC and clinical deficiencies (December 7, 2004). As there were no new pharmacology/toxicology elements, the previous P/T review still stands. However, because the label format has changed, the previous label is no longer relevant. The P/T elements to be contained in the new label are listed below.

P/T Label Elements

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA Gel. ZIANA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ZIANA Gel was tested for maternal and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA Gel at 600 mg/kg/day (approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA Gel for two weeks prior to artificial insemination and continuing until gestation day 18, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA Gel applied daily to a 60 kg person.

Clindamycin
Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin up to 180 mg/kg/day (175 and 88 times the amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin
In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (~ 78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on a body surface area comparison.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
ZIANA Gel
Carcinogenicity, mutagenicity and impairment of fertility testing of ZIANA Gel has not been performed in any species.

Clindamycin
The carcinogenicity of a 1% clindamycin phosphate gel similar to ZIANA Gel was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 13 and 72 times higher than the human dose of clindamycin phosphate from ZIANA Gel, assuming complete absorption and based on a body surface area comparison. No significant increase in tumors was noted in the treated animals. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA Gel applied daily to a 60 kg person.
Fertility (Segment 1) studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 290 times the amount of clindamycin delivered from the recommended clinical dose for ZIANA Gel, based on a body surface area comparison) revealed no effects on fertility or mating ability.

Tretinoin
In two independent studies with long-term topical application of tretinoin in mice, carcinogenicity was not observed. In both studies, tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years. No carcinogenicity was observed with maximum effects of dermal amyloidosis in the basal layer of the skin.
Tretinoin has been shown to enhance photoco-carcinogenicity in properly performed specific studies, employing concurrent or intercurrent exposure to the drug and UV radiation. The contribution of clindamycin to that effect is unknown. Although the significance of these studies to humans is not clear, patients should minimize exposure to sun.
The genotoxic potential of tretinoin was evaluated in an in vitro Ames Salmonella reversion test and an in vitro chromosomal aberration assay in Chinese hamster ovary cells. Both tests were negative.

In oral Segment 1 studies in rats treated with tretinoin, the no-observed-effect-level was 2 mg/kg/day (~78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

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/s/

Jill Merrill
10/17/2006 02:24:49 PM
PHARMACOLOGIST

revised as per your instructions

Paul Brown
10/19/2006 02:01:27 PM
PHARMACOLOGIST

Appears This Way
On Original

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:	**21-739**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**2/06/04**
PRODUCT:	**ClinRA (1% clindamycin, 0.025% tretinoin) Gel**
INTENDED CLINICAL POPULATION:	**Patients with acne vulgaris**
SPONSOR:	**Dow Pharmaceutical Sciences**
DOCUMENTS REVIEWED:	**electronic submission**
REVIEW DIVISION:	**Division of Dermatological and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Jill Merrill**
PHARM/TOX SUPERVISOR:	**Paul Brown**
DIVISION DIRECTOR:	**Dr. Jonathan Wilkin**
PROJECT MANAGER:	**Jacquelyn Smith**

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

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – ClinRA Gel for the treatment of acne vulgaris is approvable from a pharmacological/toxicological perspective

B. Recommendation for nonclinical studies – No additional nonclinical studies are recommended for ClinRA Gel at this time.

C. Recommendations on labeling – A number of changes were recommended to the sponsor's proposed labeling. These changes are detailed in the Overall Conclusions and Recommendations.

II. Summary of nonclinical findings

- Brief overview of nonclinical findings - A dosage level of 125 mg ClinRA Gel/kg/day, the highest dose tested, was considered to be the NOAEL following 13 weeks of topical application in Hanford minipigs. A dosage level of 600 mg ClinRA Gel/kg/day, the highest dose tested, was considered to be the NOAEL for maternal and developmental toxicity following dermal application for 2 weeks prior to artificial insemination and continuing until gestation day 18 in New Zealand white rabbits. ClinRA Gel was not considered to be a primary skin irritant or a primary eye irritant in rabbits as defined in the appropriate FHSA regulation. ClinRA Gel was not a sensitizer when tested in the guinea pig maximization test. There does not appear to be any reason to expect the proposed combination of clindamycin phosphate and tretinoin to have greater toxicity than other previously approved topical formulations of either clindamycin phosphate or tretinoin.

- Pharmacologic activity- Clindamycin phosphate is a lincosamide antibiotic; Tretinoin is a retinoid.

- Nonclinical safety issues relevant to clinical use - The most pronounced toxicity associated with clindamycin has been pseudomembranous colitis. This is believed to be caused by the overgrowth of a toxin producing *Clostridium difficile*. However, because systemic exposure following topical application of clindamycin is low, it is not anticipated that subjects receiving treatment with ClinRA Gel will be affected. A warning about this adverse effect is included in the labels of currently approved formulations of clindamycin and will be included in the ClinRA Gel label. Tretinoin, like other retinoids, is teratogenic and embryotoxic in multiple species when administered at sufficient doses and at the vulnerable gestational time period. Doses of tretinoin that do not cause morphological changes in offspring may cause behavioral effects in the developing animals. Topical application of tretinoin appears to be less likely to

result in teratogenic or other effects probably due to lower systemic and embryo exposure to tretinoin by the topical route than by the oral route.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-739
Review number: 1
Sequence number/date/type of submission: 000/2-6-04/original NDA submission
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Dow Pharmaceutical Sciences, Petaluma, CA
Manufacturer for drug substance:

Clindamycin phosphate:
manufacturer)

b(4)

manufacturer)

b(4)

Tretinoin:

b(4)

Reviewer name: Jill C Merrill
Division name: Dermatological and Dental Drug Products
HFD #: 540
Review completion date: 11-17-04

Drug:

Trade name: ClinRA Gel

Generic name: Clindamycin phosphate and tretinoin (retinoic acid, all-*trans*-retinoic acid)

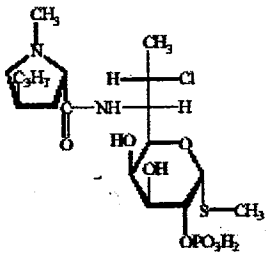
Chemical name: Clindamycin phosphate: methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate)

Tretinoin: 3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (all-*trans* form)

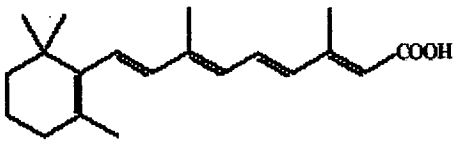
CAS registry number: clindamycin phosphate: 24729-96-2; tretinoin: 302-79-4

Molecular formula/molecular weight:
Clindamycin phosphate: $C_{18}H_{34}ClN_2O_8PS$ / MW = 504.97
Tretinoin: $C_{20}H_{28}O_2$ / MW = 300.44

Structure:



Clindamycin phosphate



Tretinoin

Relevant INDs/NDAs/DMFs:

IND 65,531 (clindamycin phosphate and tretinoin)

Drug class: antibiotic/retinoid

Intended clinical population: patients with acne vulgaris

Clinical formulation: gel with clindamycin phosphate equivalent to 1% clindamycin and 0.025% tretinoin

Component	% (w/w)
Clindamycin phosphate, USP	1.20
Tretinoin, USP	0.025
Butylated hydroxytoluene, NF	
Citric acid [redacted], USP	
Edetate disodium, USP	
Methylparaben, NF	
Propylparaben, NF	
Polysorbate 80, NF	
Glycerin, USP	
Tromethamine [redacted] USP	
[redacted] 981, NF	
Purified water, USP	

b(4)

Route of administration: topical to the skin

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

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-739 are owned by Dow Pharmaceutical Sciences or are data for which Dow Pharmaceutical Sciences has obtained a written right of reference. Any information or data necessary for approval of NDA 21-739 that Dow Pharmaceutical Sciences does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Dow Pharmaceutical Sciences does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-739.]

Studies reviewed within this submission:

FSHA Acute oral toxicity screen (7001-G2HP-07-02)
13-Week dermal toxicity study of ClinRA Gel in minipigs with 4-week recovery period (7001-G2HP-05-02)
A dermal dose range-finding developmental toxicity study in New Zealand white rabbits with 2-weeks pretreatment with ClinRA Gel (7001-G2HP-04-02)
Dermal development toxicity (Segment I/II) with a 2-week pre-treatment period (7001-G2HP-06-02)
FHSA Primary skin irritation (7001-G2HP-01-02)
FHSA Primary eye irritation (7001-G2HP-03-02)
Maximization sensitization test (ISO) (7001-G2HP-02-02)

Studies <u>not</u> reviewed within this submission:

Dermal carcinogenicity study in mice with clindamycin phosphate [redacted] Report No. 11484). This study was previously submitted to [redacted] on June 11, 1999 and reviewed under SN008. b(4)

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Clindamycin phosphate:
Clindamycin binds to the 50S subunit of bacterial ribosomes and thereby interferes with bacterial protein synthesis. Clindamycin is primarily bacteriostatic. Clindamycin is active against gram positive cocci and most anaerobic gram negative organisms. Its activity against the anaerobe *Propionibacterium acnes* may account for its effectiveness in the treatment of acne vulgaris.

Tretinoin:
Tretinoin, also known as all-trans-retinoic acid, is a member of the retinoid family of compounds and is an endogenous metabolite of vitamin A. Tretinoin, like other retinoids, regulates gene transcription through the interaction with intracellular retinoic acid receptors. Retinoids impact a variety of cellular and physiologic processes. The exact mechanism by which retinoids are beneficial in acne is unknown. The sebolytic, keratolytic and anti-inflammatory activity of retinoids may contribute to their effectiveness in treating acne.

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of the peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increases the turnover of follicular epithelial cells causing extrusion of the comedones.

Drug activity related to proposed indication:
The efficacy of clindamycin phosphate in the treatment of acne lies in its ability to inhibit the growth of *P. acnes*. Overgrowth of *P. acnes* and the ensuing host inflammatory response are believed to be important in the pathogenesis of acne. Current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Tretinoin also stimulates mitotic activity and increases the turnover of follicular epithelial cells causing extrusion of the comedones.

2.6.2.3 Secondary pharmacodynamics

No studies to address secondary pharmacodynamics were included in this submission.

2.6.2.4 Safety pharmacology

A transient neuromuscular blockade is a recognized side effect of clinical use of antibiotics, including clindamycin. Extensive analysis of the blockade has led to the conclusion that clindamycin exerts its main effect post-synaptically at the neuromuscular junction, with a minor component of the inhibition also occurring pre-synaptically. The basis for these effects has been determined to be the lipophilic nature of the structure of clindamycin, which allows the molecule to compete with calcium for entry into nerve terminals, resulting in interference with nerve transmission. The effect of clindamycin on neuromuscular transmission has potential relevance to gastrointestinal smooth muscle function and the development of enterocolitis. However, because systemic exposure following topical application of clindamycin is low, it is not anticipated that subjects receiving treatment with clindamycin phosphate will be affected.

2.6.2.5 Pharmacodynamic drug interactions

No studies to address pharmacodynamic drug interactions were included in this submission.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

This section is not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Clindamycin phosphate:
Studies in rats and dogs show that clindamycin is readily absorbed from the gastrointestinal tract and is excreted in the urine and feces (Sun and His, 1973; Sun, 1973). In rat, the products excreted in the urine were 53% unchanged clindamycin, 31% clindamycin sulfoxide and 15% N- demethyl clindamycin. In dog, the products excreted in the urine were 36% unchanged clindamycin, 28% clindamycin sulfoxide, 28% clindamycin glucuronide and 9% N-demethyl clindamycin. Topical application in the rat and pig show that clindamycin can be retained in the skin and is released into the blood for several days after drug application.

Absorption of clindamycin from topical formulations has been measured in humans and ranges from undetectable up to approximately 7.5% of the applied clindamycin (Eller *et al.*,1989). In humans approximately 10% of clindamycin administered is excreted unchanged in the urine. Clindamycin is metabolized in humans to N- demethyl clindamycin and clindamycin sulfoxide, which are excreted in the urine and bile.

Tretinoin:
Tretinoin can be absorbed percutaneously. One study found that between 5 and 7 percent of the tretinoin in a cream formulation was absorbed in humans over a 10 hour period (Franz and Lehman,1990). Slightly more tretinoin was absorbed in diseased skin (acne) compared to normal skin. Tretinoin is metabolized by several pathways (Allen and Bloxham, 1989; Lucek and Colburn, 1985). It can be conjugated with taurine followed by elimination in the bile. It can be hydroxylated at the C- 4 in the cyclohexenyl ring and oxidized to the 4- ketone. This may then undergo conjugation. Decarboxylation of the sidechain can also occur. Tretinoin can also undergo isomerization to the 13- cis isomer of retinoic acid. The terminal elimination half- life of tretinoin in rats has been estimated to be approximately 20 minutes.

2.6.4.2 Methods of Analysis

This section is not applicable.

2.6.4.3 Absorption

Clindamycin phosphate:

The percutaneous absorption of clindamycin HCl has been studied in Yorkshire (white) and Hampshire (black) pigs (Gray *et al.*, 1983). Pigs were administered two daily applications of 3% clindamycin HCl (7.3-10.3 mg/kg/day clindamycin HCl) for 22 days. Results from this study have indicated that this drug is retained principally in the epidermis and to a much lesser extent the dermis. In pigs, accumulation and retention of clindamycin was shown to be much higher in pigmented skin of black pigs compared to white pigs, with very low levels found in urine samples at termination of dosing and up to 97 hours post treatment (0.13 to 0.63 μg/mL).

Tretinoin:

Percutaneous absorption studies in a variety of species have demonstrated that limited amounts of tretinoin are systemically absorbed following topical administration of tretinoin. Furthermore, data in the literature suggest that percutaneous absorption is higher in animals than in humans.

2.6.4.4 Distribution

Clindamycin phosphate:

Ninety percent or more of clindamycin is transported in the circulation as a complex with plasma proteins and is widely distributed in many fluids and tissues, including bone. *In vitro* studies have also demonstrated accumulation of clindamycin in polymorphonuclear leukocytes and alveolar macrophages (Hand 1990a; 1990b; Hand 1984; Voisin 1987).

Tretinoin:

Unlike the parent compound retinol, which is bound in plasma to a specific a1-globulin (retinol-binding protein), the circulatory transport of tretinoin in the plasma does not appear to be mediated by a special carrier protein, but occurs almost entirely through binding to albumin (Chytil, 1986). As with absorptive mechanisms, the absence of specific plasma transport as well as tissue storage mechanisms is likely based on a lack of requirement, given the insignificant amount of tretinoin provided in the diet. The distribution of radiolabeled tretinoin was measured in Sprague Dawley rats following topical application of 1.3-4 mg of ^{3}H-tretinoin to shaved dorsal skin (Barua, 1996). The distribution of tretinoin radioactivity in serum, liver, intestines, and kidney was determined. Peak serum concentrations reached approximately 1% within 2-4 hours of application with about 1% in the liver, 0.35% in the intestines, and 0.1% in the kidneys. Thus, none of the tissues analyzed showed significant accumulation of tretinoin following topical application of tretinoin.

2.6.4.5 Metabolism

Clindamycin phosphate:

Metabolism of clindamycin occurs via three major metabolic routes: In the Sprague Dawley rat clindamycin is metabolized to N-demethylclindamycin via N-demethylation and clindamycin sulfoxide via S-oxygenation. Both of these metabolites are biologically active when evaluated in antibacterial tests. Clindamycin sulfoxide is approximately 25% as active as clindamycin and N-demethylclindamycin is approximately 4-fold more active than clindamycin. In dogs however, the major metabolites of clindamycin are clindamycin sulfoxide and clindamycin glucuronide via glucuronic acid conjugation. In contrast to the other two metabolites of clindamycin, clindamycin glucuronide has little or no antibacterial activity (Sun 1973b).

Tretinoin:

Metabolism of tretinoin and its isomers to more polar metabolites has been shown to be mediated by Phase 1 oxidative pathways involving cytochrome P450 (CYP) activity (White, 1997) and Phase 2 glucuronide conjugation reactions. Specific CYPs have been identified which are responsible for the selective metabolism of the different tretinoin isomers (Marill, 2000, 2002). The principal metabolites of tretinoin have been identified as 4-oxo-retinoic acid (4-oxo-RA), 4-OH-RA, 18-OH-RA, and 5,6-epoxy-RA (White, 1997; Idres, 2001). Tretinoin metabolism is highly species specific . In models such as the mouse, oral tretinoin is metabolized predominantly to 4-oxo-RA (Kochhar, 1997; Kraft, 1987; Kraft, 1989), while in Swiss Hare rabbits (Tzimas, 1994) and cynomologus monkeys (Kraft, 1991), oral administration of tretinoin results in predominantly glucuronidation and only a small amount of 4-oxo-RA is produced (Kochlar, 1997).

2.6.4.6 Excretion

Clindamycin phosphate:

Elimination of clindamycin was evaluated in Sprague Dawley rats administered orally and intraperitoneally (IP) and in Beagle dogs administered orally and intramuscularly (IM) (Sun, 1973a). After oral or IP administration of clindamycin HCl in rats, 96% of the dose was recovered within 2 weeks (90% within 120 hours), with 27% excreted in the urine and 69% recovered in the feces. The rate of excretion, however, was slower following IP compared with oral administration. This was attributed to a slower initial rate of urinary excretion of clindamycin following IP injection (9.45 hr) compared to oral administration (4.3 hr) and to slower transport to the bile following IP injection. The pattern of clindamycin recovery in urine and feces of rats was similar to that found in dogs. The urinary excretion products of clindamycin HCl metabolism in Sprague Dawley rats and Beagle dogs were isolated and characterized (Sun, 1973b). In rat urine, 53% was unchanged clindamycin, 31% was clindamycin sulfoxide, and 15% was N-demethylclindamycin. In dog urine, 36% was unchanged, 28% was clindamycin sulfoxide, 28% was clindamycin glucuronide, and 9.16% was N-demethylclindamycin.

Tretinoin:

Tretinoin is not retained in tissue depots and is rapidly cleared from the body. Studies with radiolabeled material indicate that biliary excretion is the major route of elimination for tretinoin metabolites. Excretion of radiolabeled tretinoin was measured in Sprague Dawley rats following a single topical application of 1.3-4 mg of ^{3}H-tretinoin to shaved dorsal skin (Barua, 1996). During a 7-day period, considerable amounts of radioactivity were excreted in both urine and feces, 12% and 17%, respectively. The systemic absorption and excretion of tretinoin was evaluated in monkeys following a single topical application of 200 mg radiolabeled tretinoin (Franz, 1990). In Rhesus monkeys nearly 21% of topically applied radioactive tretinoin was excreted in the urine during a 7-day collection period, with more than 80% of the total urinary excretion of radioactivity occurring within the first 48 hours after administration.

2.6.4.7 Pharmacokinetic drug interactions

No studies to address pharmacokinetic drug interactions were included in this submission.

2.6.4.8 Other Pharmacokinetic Studies

No other pharmacokinetic studies were included in this submission.

2.6.4.9 Discussion and Conclusions

Literature studies to address the nonclinical pharmacokinetics of the combined drug product, ClinRA Gel, are not available. It is not expected that the combination of clindamycin phosphate and tretinoin would lead to significantly different, or new, ADME characteristics.

2.6.4.10 Tables and figures to include comparative TK summary

This section is not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

This section is not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Clindamycin phosphate:
The most pronounced toxicity associated with clindamycin has been pseudomembranous

colitis. This is believed to be caused by a toxin produced by *Clostridium difficile*. Absorption of clindamycin phosphate from topical application may be sufficient to cause colitis. While the rat and dog do not demonstrate this toxicity, it has been observed in hamsters, rabbits and humans. In the hamster, all animals given 40, 10 or 1 mg/kg topically for two weeks died from colitis (Lusk *et al.*, 1978). Four of seven animals given 0.1 mg/kg also died. A warning about this adverse effect is included in the labels of currently approved formulations of clindamycin. Long term studies in rats and dogs have been conducted and published with oral clindamycin hydrochloride and oral clindamycin palmitate hydrochloride (Gray *et al.*, 1972). The maximum tolerated dose of clindamycin hydrochloride in a one year rat study was between 300 and 600 mg/kg. No specific morphologic alteration attributed to treatment with clindamycin hydrochloride was identified. Clindamycin palmitate hydrochloride doses of 100, 300 and 600 mg/kg were well tolerated by rats in a six month study. Dogs given 30 and 100 mg/kg of clindamycin hydrochloride appeared healthy during a one year study, but dogs receiving 600 mg/kg were clinically sick. Dogs in all three groups had elevated serum glutamic-pyruvic transaminase levels. Dogs receiving 600 mg/kg had bile stained ulcers of the gall bladder upon necropsy. Clindamycin palmitate hydrochloride doses of 30, 100 and 300 mg/kg were well tolerated by dogs in a six month study.
Gray *et al.* (1974) also studied the toxicity of clindamycin phosphate when given intravenously to dogs for up to 30 days. Doses of 60 and 120 mg/kg did not produce any drug-related effects, including no changes observed in hematology, clinical chemistry and urinalysis parameters.

Tretinoin:
The results of several studies of tretinoin toxicity have been published. A survey of several acute toxicity studies showed LD_{50} values in mice of about 2200 mg/kg for oral tretinoin and 790 mg/kg for intraperitoneal tretinoin (Kamm,1982). In rats the LD_{50} values were about 2000 mg/kg for oral tretinoin and 790 mg/kg for intraperitoneal tretinoin.

Studies in mice have been conducted with tretinoin by the oral or intraperitoneal route for up to 22 days. Dose related toxicity was observed in mice gavaged with 2.5, 10 and 30 mg/kg/day (Lindamood *et al.*, 1990). The effects included weight loss, skin scaling, alopecia, bone toxicity including fractures, increased spleen weight, enlarged lymph nodes, elevated serum alkaline phosphatase and increased white blood cell counts. Histopathological findings included atrophy of the sebaceous glands, epidermal hyperplasia, dermal inflammation, hematopoietic cell proliferation in the spleen, bone marrow hypercellularity, thymic atrophy, hematopoietic cell foci in the liver, cytoplasmic vacuolation of hepatocytes, hypertrophy of the adrenal cortex, hyperplasia of squamous epithelium of the forestomach, inflammation of the forestomach and glandular stomach, testicular atrophy and bone thinning.

Repeat dose studies with tretinoin have been conducted by the oral route for up to 13 weeks in rats and dogs. In one study, growth depression, anemia, elevated alkaline phosphatase, bone fractures and testicular degeneration were observed in rats at doses of 14 and 50 mg/kg/day (Kurtz *et al.*, 1984). The effects were severe at 50 mg/kg and all

rats at this dose were euthanized during the third week of treatment. Another 13-week study in rats showed that oral doses of 5 mg/kg produced the symptoms of hair loss, dermal and mucosal alterations and loss of body weight. In this study approximately 20% of the animals died at a dose of 50 mg/kg (Kretzschmar and Leuschner, 1975). In a 13-week study in dogs, toxic symptoms were induced at 5 mg/kg and 50 mg/kg was lethal starting at the 11th week (Kretzschmar and Leuschner, 1975). Studies on the dermal toxicity of tretinoin in the mouse, rat and rabbit have been published. Essentially no systemic toxicity has been observed in these studies. Hairless mice treated 3 times a week for up to 2 years with 0.025% tretinoin showed epidermal hyperplasia with focal areas of apparently new collagen formation (Kligman *et al.*, 1992). Studies in rats using daily treatment for 7 weeks of 0.05 and 0.1% formulations of tretinoin resulted in dose dependent erythema by the second week. There was a slight edema of the upper skin layers and acanthosis and hyperkeratosis were observed in the skin (Herold *et al.*. 1975). Similar findings were observed in the rabbit.

Genetic toxicology:

Clindamycin phosphate:

Two genotoxicity tests were performed for clindamycin (Snyder, 2001. Although this reference is available in the open literature, it references the 1999 Physician's Desk Reference. No data was provided, only the conclusion). Clindamycin was found not to be a mutagen using the Ames *Salmonella* reversion test, and was negative in an *in vivo* cytogenetics assay.

Tretinoin:

An *in vitro* Ames assay of tretinoin was conducted in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (Kamm, 1982). Doses of up to 2 mg/plate were tested, with and without metabolic activation. Tretinoin was negative for genotoxicity in this assay. Retinoic acid was evaluated in the CHO HGPRT assay as part of a published study investigating the ability of retinoic acid and retinol to inhibit DMBA- induced genotoxicity (Budroe *et al.*, 1988). Retinoic acid alone did not cause an increase in mutations in the presence or absence of metabolic activation. Concentrations of up to 25 μM were tested with metabolic activation and concentrations up to 100 μM were tested without metabolic activation. Retinoic acid was not toxic to the CHO cells with metabolic activation up to the highest dose of 25 μM. In the absence of metabolic activation, the high dose of 100 μM retinoic acid produced about an 80% reduction in survival of the CHO cells.

Genetic toxicology conclusions:

Clindamycin and tretinoin have been negative in genotoxicity studies conducted to date.

In some cases these studies would not meet current ICH recommendations for how such studies should be conducted. However, the negative results do not raise any concerns and so additional genotoxicity studies are probably not necessary at this time.

Carcinogenicity:

Clindamycin:
The sponsor has not conducted any new carcinogenicity studies with clindamycin phosphate. However, they have obtained the right of reference to a dermal carcinogenicity study conducted in mice with a clindamycin 1% gel product that was submitted to [redacted] on June 11, 1999 ([redacted] Report No. 11484, Serial Submission No. 008). A summary of this previously reviewed study appears below: b(4)

Doses were selected to provide a maximum dose which would not be expected to produce overt nephrotoxicity or more than a 10% body weight loss with continuous dosing in the mouse through a lifetime. Four groups of 60 male and 60 female CD-1 mice were treated by dermal application daily for 2 years with the following test articles:

Test Article	Dose of Test Article	Dose of Clindamycin
Clindamycin 1% Gel	2.7 mL/kg/day	27 mg/kg/day
Clindamycin 1% Gel	15 mL/kg/day	150 mg/kg/day
Placebo Gel (2 controls)	15 mL/kg/day	0 mg/kg/day

No attempt was made to prevent ingestion of the test articles. The body weight of each animal was recorded once a week for the first 14 weeks and approximately once every 2 weeks from week 16 to the end of the study. The quantity of feed consumed by each animal was recorded once a week for the first 14 weeks and approximately once every 4 weeks from week 16 to the end of the study. All surviving animals were terminated and necropsied. All animals found dead were also subjected to a full gross necropsy, which included a complete examination of all internal organs and tissues of the body.

The histological findings were typical for mice of their age and strain in a study of this type and duration. Carcinomas of the parotid salivary gland were seen in 1 male treated with 2.7 mL/kg/day and 1 male treated with 15 mL/kg/day clindamycin 1% gel. These are considered rare spontaneous tumors and were not seen in control CD-1 mice in the study. However, this study does not establish a clear association between these tumors and clindamycin phosphate treatment. As noted above, no attempt was made to prevent ingestion of the test articles. According to published reports, salivary gland inflammation has been observed in rats treated orally with clindamycin hydrochloride and nuclear atypia of salivary gland cells has been described in rats receiving clindamycin palmitate hydrochloride in the diet. These effects have been ascribed to opportunistic infections of the salivary gland. In particular, this type of lesion has been attributed to coronavirus infections in rodents. It may be possible that these effects are due to the ingestion of clindamycin with subsequent alterations of the bacterial flora of the mouth leading to opportunistic infections. [redacted] quoted a spontaneous incidence of 2/478 salivary gland tumors in female CD-1 mice between 21-24 months of age and 0/480 in males of

the same age. Despite the rarity of these tumors, it is considered that these tumors cannot be attributed to an effect from clindamycin 1% gel. Overall the total incidence of tumors and animals with tumors varied between groups but did not show a relationship to the clindamycin 1% gel.

The study is acceptable as an evaluation of the carcinogenicity of clindamycin phosphate by the dermal route for the drug product under review. The doses used in the study appear to have achieved an MTD based on dermal criteria. The doses are approximately 13 and 72 fold higher than the anticipated maximum human exposure assuming complete absorption based on a mg/m^2 comparison and appear to be the maximum feasible amount of material that could be applied.

The executive carcinogenicity assessment committee met on June 6, 2000 and discussed the results of this study. The committee concluded that the study was adequate for the evaluation of topical clindamycin phosphate . The committee recommended that the study be described in the label as showing no significant increase in tumors.

Photocarcinogenicity:

Although the sponsor has submitted a literature reference (Gray *et al.*, 1972) in which rats administered oral clindamycin HCl at concentrations of 30 mg/kg, 100 mg/kg, and 300 mg/kg for 8 months did not display signs of phototoxicity following exposure to direct sunlight for 2.75 hours, this study does not qualify as an acceptable photocarcinogenicity study.

Tretinoin:
The sponsor has submitted several literature references on the photocarcinogenicity and carcinogenicity of tretinoin. These are reviewed below.

Photocarcinogenicity
Forbes (1979) demonstrated that essentially non-irritating concentrations of tretinoin promoted tumor formation in hairless mice when applied topically following UVB irradiation. Following a 2-week pre-treatment with tretinoin, mice were dosed daily with 0.001% (0.0002 mg tretinoin/day) or 0.01% (0.002 mg tretinoin/day) tretinoin immediately after a 2 hour UV exposure. Tretinoin treated animals developed skin tumors much earlier and in greater numbers than control animals. Mice receiving 0.01% tretinoin developed skin tumors within 20 weeks and displayed moderate epidermal hyperplasia with some scaling and transient erythema, while mice receiving 0.001% tretinoin developed tumors within 25 weeks. By 35 weeks the number of skin tumors in mice receiving 0.01% or 0.001% tretinoin was similar. In contrast, mice receiving only UV irradiation developed skin tumors beginning at 40 weeks, with an incidence of less than 25% compared to tretinoin treated animals at 50 weeks.

Halliday (2000) reports topically applied tretinoin was shown to enhance photocarcinogenesis in both lightly pigmented and albino mice. Mice were exposed to daily solar-simulated unltraviolet radiation immediately followed by treatment with

0.05% tretinoin (0.01 mg tretinoin/day). Treatments were performed 5 days per week for 4 weeks, then three days per week thereafter. Tretinoin application decreased the latency period, reduced the probability that a mouse would survive without a tumor, and increased the number of tumors per mouse. All tumors induced were squamous cell carcinomas, and the skin between the tumors on mice treated with tretinoin was found to contain carcinoma *in situ* upon histologic diagnosis. Although the extent of tumor formation was less in pigmented mice that were tanned by the effects of tretinoin and UVR, this did not preclude the increased effect of retinoic acid on photocarcinogenesis. In contrast, other studies with tretinoin have shown either no effect or an inhibition of tumorigenesis (Epstein 1981; Kligman 1981; Kligman 1987). The ambiguity of these studies on the potential for tretinoin to enhance or inhibit photocarcinogenesis, is most likely attributed to variables within the study designs. The significance of the chosen vehicle and presence of antioxidants on the photocarcinogenic potential of tretinoin was investigated (Kligman, 1987), the significance of pigmentation in study animals was demonstrated (Halliday, 2000), the significance of time of tretinoin application in relation to the time of irradiation was demonstrated (Connor, 1983), and the spectral distribution and dose of incident UV radiation was studied (Forbes, 1979, 1981). It is concluded that tretinoin enhances photocarcinogenicity in properly performed specific studies, using concurrent or intercurrent exposure to the drug and UV radiation.

Carcinogenicity:

Despite the equivocal results on the ability of tretinoin to enhance photocarcinogenesis, there is no evidence in animals that topical tretinoin itself is a carcinogen. In the above photocarcinogenesis studies where control animals were treated with tretinoin in the absence of UV irradiation, none of the control animals treated with tretinoin in the absence of UVR developed any tumors (Halliday *et al.*, 2000, Connor *et al.*, 1983, Kligman and Kligman, 1981). In two additional studies with long-term topical application of tretinoin to mice, carcinogenicity was not observed (Tsubura 1979; Kligman 1992). In both studies, tretinoin was administered topically (0.025% or 0.1%) three times per week for up to two years. No carcinogenicity was observed with maximum effects of dermal amyloidosis.

Reproductive toxicology:

The sponsor submitted several literature references on the reproductive and developmental toxicity of clindamycin and tretinoin. These are reviewed below.

Clindamycin phosphate:

The teratogenic potential of clindamycin phosphate has been previously investigated in SD rats and ICR and CF1 mice (Bollert *et al.*, 1974). Each species was injected subcutaneously with 100 and 180 mg/kg on gestation days 6 through 15. There was no indication of teratogenic effects and no detrimental effect on reproduction. Other reproductive and developmental toxicity studies have been conducted with oral clindamycin hydrochloride and clindamycin palmitate (Gray *et al.*, 1972). CD/spf rats

and CD- 1/ spf mice dosed on gestation days 6 to 15 with up to 200 mg/kg or TUC/SD rats dosed on gestation days 6 to 16 with up to 100 mg/kg clindamycin hydrochloride showed no signs of teratogenicity. TUC/SD rats dosed with up to 600 mg/kg clindamycin palmitate during days 6 to 15 of gestation did not show any signs of teratogenicity. In a study examining reproductive performance, Sprague-Dawley rats were given up to 60 mg/kg clindamycin hydrochloride and up to 300 mg/kg clindamycin palmitate in the diet (Gray *et al.*, 1972). In these studies, treatment was started in male rats at 40 days of age and in the females, 14 days before breeding. The females treated with clindamycin hydrochloride conceived at a slightly lower rate and their young were slightly smaller at weaning than the untreated controls. Otherwise no effect on reproductive performance was noted.

Tretinoin:

The teratogenic potential of tretinoin was evaluated in Wistar rats by administering doses of 1, 2.5, 5 and 10 mg/kg by gavage on gestation days 6 through 15 (Seegmiller *et al.*, 1997). An increase in cleft palate was observed in fetuses of the 10 mg/kg group. Incomplete ossification of the cranial bones and supernumerary ribs were noted at a significantly higher incidence in the fetuses of the 5 and 10 mg/kg group. Other skeletal abnormalities were also noted in the tretinoin treated groups. This same reference (Seegmiller *et al.*, 1997) describes studies in which Wistar rats were treated with topical tretinoin at doses of 1, 2.5, 5, 10 and 20 mg/kg on gestation days 6 through 16. Dosing was discontinued early in the 10 and 20 mg/ kg groups because of excessive toxicity to the dams. Weight gain in the dams treated with 2.5 and 5 mg/kg was significantly decreased compared to control. Mean fetal weight was lower in the 5 mg/kg group. Increased incidences of supernumerary ribs and rudimentary ribs were noted in the fetuses from the 2.5 and 5 mg/ kg groups. In studies by Nolen (1986), female Sprague-Dawley rats were treated orally with 5 mg/kg tretinoin during gestations days 8-10 or with 2.5 or 5 mg/kg on gestations days 11-13 or 14-16 or with 2, 4 or 6 mg/ kg on gestations days 14-16. The doses of 5 and 6 mg/kg were not embryotoxic but many of the pups from dams treated on gestation days 11-13 died within the first four postnatal days. Behavioral alterations were observed in the pups. Pups from dams treated with 5 mg/kg tretinoin on gestation days 8-10, 11-13 or 14-16 and 2. 5 or 6 mg/kg on gestation days 14-16 had a delayed negative geotropism response. Increased motor activity and either an earlier or later onset of the auditory startle response were also observed in some tretinoin treated animals.

Forelimb placing was delayed in pups from dams treated with 2.5 mg/kg on gestation days 11-13 or 5 mg/kg on gestation days 14-16. Males from dams treated with 2.5 or 5 mg/kg tretinoin on gestation days 14- 16 showed some impairment of their ability to successfully complete a maze. Rats from dams treated with tretinoin on gestation days 14-16 had impaired performance in an active avoidance test compared to control. The authors concluded that tretinoin caused behavioral changes at doses below those producing morphological defects. A paper by Nishimura *et al.*, 2001 describes effects of 5 mg/ kg oral tretinoin administered during gestational days 14-16 from studies conducted in 28 different Japanese laboratories. The effects on the offspring included

decreased viability, increased minor anomalies of the paw and nail, delayed pinna detachment, negative geotaxis, impaired mid air righting and less frequent rearing and grooming behaviors.

A paper by Holson *et al.,* 2001 describes reproductive toxicity studies conducted in Long- Evans and Sprague-Dawley rats. In these studies the dams were treated orally with a tretinoin dose of 2.5 mg/kg/day during days 11-13 of gestation or with 10 mg/kg/day during days 14-16 of gestation. Tretinoin caused decreased neonatal weight in the litters from dams treated during gestation days 11-13 and increased neonatal mortality in liters from dams treated either during gestation day 11-13 or 14-16. Behavioral alterations were observed in the pups. Surface righting was impaired in pups from dams treated during gestation days 11-13. Brain weights in the pups from tretinoin treated dams were slightly but significantly decreased compared to control when measured on postnatal day 35. Much of this decrease appeared to be correlated with the decreased body weight. However, even after adjusting for body weight, exposure on gestation days 11-13 reduced the weight of the cerebellar vermis while exposure on gestation days 14-16 reduced the weight of the cerebellar hemispheres. Christian *et al.,* 1997 studied the effects of topical tretinoin in New Zealand white rabbits at doses of 0.05 and 0.5 mg/kg. Animals treated with 0.5 mg/kg had increased abortions although these animals generally had severe skin irritation, weight loss and reduced feed consumption. Increased resorptions and reduced fetal body weight were also noted at this dose. Fetal abnormalities such as open eyelids, cleft palate, irregular nasal suture, fused sternbrae and irregularly shaped scapulae were noted in the tretinoin treated groups. The authors did not consider these findings to be related to tretinoin, however, since they either did not follow a dose response or were within historical control ranges. A review of tretinoin reproductive toxicity (Kochhar and Christian, 1997) notes that in a study in Wistar rats an oral dose of 2.5 mg/kg on gestation days 6 through 16 produced one occurrence of cleft palate. A dose related increase in resorptions was also noted in this study. Other studies show that higher doses produce an increasing frequency of cleft palate in Wistar rats. This review also notes that a study in cynomolgus monkeys showed craniofacial malformations at a dose of 10 mg/kg and a dose-related increase in resorptions when tretinoin was administered from gestation days 10 to 24. Tretinoin also leads to fetal abnormalities in mice, rabbits and hamsters.

The effects of oral tretinoin are dose dependent. Exposure during early post-implantation (gestation days 8-10) generally resulted in craniofacial and central nervous system effects while exposure during gestation days 12- 14 resulted in limb and genitourinary defects. Kochhar and Christian (1997) concluded that topical application of tretinoin was not teratogenic although some of the studies showed dose-related increases in skeletal abnormalities in rats and rabbits as well as decreased fetal weight and increased resorptions.

Reproductive and developmental toxicology conclusions:
Tretinoin, like other retinoids, is teratogenic and embryotoxic in multiple species when administered at sufficient doses and at the vulnerable gestational time period. Doses of tretinoin that do not cause morphological changes in offspring may cause behavioral

effects in the developing animals. Topical application of tretinoin appears to be less likely to result in teratogenic or other effects probably due to lower systemic and embryo exposure to tretinoin by the topical route than by the oral route. At the pre-IND meeting for this drug, it was recommended that a combined segment I/II study be conducted in a nonrodent model to assure steady state systemic exposures at the beginning of the period of organogenesis. The sponsor has conducted a dermal developmental toxicity study in rabbits with ClinRA Gel and with the individual active ingredients at the same concentrations that they occur in the ClinRA Gel. The animals were treated daily beginning 14 days prior to insemination and continuing through gestation day 18. Based on the results of this study, a dosage level of 600 mg/kg/day ClinRA Gel was considered to be the no-observed-adverse-effect-level for systemic maternal and developmental toxicity.

Special toxicology:

Three special toxicology studies were performed by the sponsor with ClinRA Gel and are reviewed in a subsequent section of this review. The three studies were primary skin irritation, primary eye irritation, and a guinea pig maximization sensitization test. Under the conditions tested, the proposed clinical formulation was not a primary skin or eye irritant in rabbits and was not a sensitizer in guinea pigs.

2.6.6.2 Single-dose toxicity

Study title: Acute oral toxicity of ClinRA Gel in rats

Key study findings: At an oral dose level of 5000 mg/kg of body weight the test article did not cause mortality or gross signs of toxicity when administered to five male and five female Sprague Dawley rats. Under the conditions of the test, the LD_{50} is greater than 5000 mg/kg.
Laboratory Study no.: X2L121G
Sponsor Study no.: 7001-G2HP-07-02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: December 12, 2002
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: ClinRA Gel, lot# 776

Methods

An oral dose level of 5000 mg/kg of body weight was administered undiluted by gavage to 5 male and 5 female Sprague Dawley rats (7-10 weeks of age). One male and one female were dosed with an equivalent volume of deionized water as a control. All animals were observed on the day of dosing and at least once each day for 14 days. The animals were observed for clinical signs of toxicity such as unkempt appearance, altered feeding habits, weight loss and other signs of distress or physical depression. All animals

were euthanized by IP injection of Euthasol (0.5 mL). A gross necropsy was performed on each animal at the end of the study.

Results
All of the animals remained healthy throughout the study and survived until scheduled euthanasia. No toxic signs were observed in animals treated with the test article or control article during the duration of the test.

Conclusions:
At an oral dose level of 5000 mg/kg of body weight the test article did not cause mortality or gross signs of toxicity when administered to five male and five female Sprague Dawley rats. Under the conditions of the test, the LD_{50} is greater than 5000 mg/kg.

2.6.6.3 Repeat-dose toxicity

Study Title: A 13-week dermal toxicity study with a 4-week recovery phase in Hanford minipigs with ClinRA Gel

Key study findings: Local irritation was observed in all treatment groups with a slightly higher incidence and severity of erythema observed in the 125 mg formulation/kg/day ClinRA, ClinRA with tretinoin and ClinRA with clindamycin groups. No signs of systemic toxicity were noted at any dosage level tested. The dosage level of 125 mg formulation/kg/day (2750 mg/m^2/day) was considered a no-observed-adverse-effect level (NOAEL) for the 13-week administration of ClinRA in Hanford minipigs.

Laboratory Study no.: 3551.21
Sponsor Study no.: 7001-G2HP-05-02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: August 13, 2002
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #: ClinRA Gel, lot# LB-157

Methods

Hanford minipigs (~9-22 weeks of age) were randomly assigned to one of six groups with the following study design:

Group	# of animals		Material	Formulation Dose Volume (mL/kg/day)	Formulation Dosage Level (mg/kg/day)	Tretinoin Dosage Level (mg/kg/day)	Clindamycin Dosage Level (mg/kg/day)
	Male	Female					
1	6	6	ClinRA Vehicle Gel	0.10	0	0	0
2	6	6	ClinRA Gel	0.02	25	0.005	0.2
3	6	6	ClinRA Gel	0.06	75	0.015	0.6
4	6	6	ClinRA Gel	0.10	125	0.025	1.0
5	6	6	ClinRA Gel w/Tretinoin Only (0.025%)	0.10	125	0.025	0
6	6	6	ClinRA Gel w/ Clindamycin only (1.0%)	0.10	125	0	1.0

The test article and vehicle control were administered topically to the appropriate animals on a daily basis for 13 weeks, followed by a 4-week recovery period. General health, mortality and moribundity checks were conducted twice daily. Detailed clinical observations and individual body weights were performed weekly, beginning on study day 0, and prior to scheduled euthanasia. Dermal scoring was performed twice per week during the dosing phase, once per week during the recovery phase and on the day of scheduled euthanasia. Hematology, coagulation and clinical chemistry parameters were evaluated once prior to in-life initiation and near conclusion of the dosing and recovery phases. Ophthalmological examinations were performed once prior to in-life initiation and just prior to the end of the dosing phase. Toxicokinetic blood samples were collected on study days 0 and 89 and the plasma samples were shipped on dry ice, via overnight courier to [redacted] for analysis. All animals were subjected to a complete gross necropsy at the end of the dosing or recovery phase. Fresh organ weights obtained for surviving animals and selected tissues were preserved from all animals. All tissues collected at necropsy from all animals were examined microscopically for abnormalities.

b(4)

Results

Mortality: All animals survived to scheduled euthanasia.

Clinical signs: There were no clinical signs of toxicity in the test article-treated animals during the main study or recovery phases. Clinical signs including swelling, scab(s) and open lesions were noted in the main study animals. However, these findings were also observed in the vehicle group and did not follow any pattern which would indicate a relationship to treatment. Dermal irritation was observed in the vehice control and test article-treated animals using the Draize scale. Grade 1 erythema was noted in nine out of 12 (75%) animals in the vehicle group, all (100%) of the animals in the ClinRA treated and 125 mg formulation/kg/day ClinRA with Tretinoin group, and 11 (92%) animals in the 125 mg formulation/kg/day ClinRA with Clindamycin group. Grade 2 erythema was noted in three (25%) animals each in the vehicle and 25, 75, and 125 mg formulation/kg/day ClinRA groups; seven (58%) of the 125 mg formulation/kg/day ClinRA with Tretinoin animals and four (33%) of the 125 mg formulation/kg/day ClinRA with Clindamycin animals. Grade 3 erythema was observed in one (8%) of the 125 mg formulation/kg/day ClinRA animals, five (42%) of the 125 mg formulation/kg/day with Tretinoin animals and one (8%) of the 125 mg formulation/kg/day ClinRA with Clindamycin animals. A slightly higher incidence and severity of erythema was observed in the 125 mg formulation/kg/day ClinRA, ClinRA with Tretinoin and ClinRA with Clindamycin groups.

Body weights: There were no toxicologically meaningful differences among the groups with regards to mean absolute body weights or body weight changes.

Feed consumption: not measured

Ophthalmoscopy: There were no toxicologically meaningful differences among the groups with regards to ocular abnormalities.

EKG: not measured

Hematology: There were no toxicologically meaningful differences among the groups with regards to hematology and coagulation parameters.

Clinical chemistry: There were no toxicologically meaningful differences among the groups with regards to clinical chemistry.

Urinalysis: not measured

Gross pathology: Gross necropsy evaluations did not reveal any findings indicating any effects of the test articles. Cysts were observed on the epididymides of two males from the 75 mg/kg/day ClinRA group following the main study and both 75 mg/kg/day ClinRA recovery males. However, this finding is not considered to be toxicologically meaningful since the occurrence was not observed in the high-dose (125 mg/kg/day) ClinRA group, the ClinRA with Tretinoin group or the ClinRA with Clindamycin group. A variety of other gross changes were observed, but these tended to be of low incidence and randomly distributed among the study groups.

Organ weights: There were no toxicologically meaningful or statistically significant differences in absolute organ weights or organ-to-body weight ratios.

Histopathology: There were no test material associated lesions or significant tissue changes noted at the site of dermal application of the vehicle control or test articles. The lesions observed were common for this age and type of minipig. A slight increase in the incidence of mild or minimal parakeratosis in the treated skin section was observed in some dose groups compared to the controls; however, mild to minimal parakeratosis was also noted at a higher incidence in the untreated skin tissue compared to the treated skin tissue samples. Therefore, the minimal to mild parakeratosis observed in the treated skin tissue samples was an incidental background lesion of no significance in the minipigs in this study.

Toxicokinetics: Concentrations of clindamycin phosphate, tretinoin and its metabolites in the plasma samples collected, were generally not detectable or were below the lower limit of quantitation of 1.0 ng/mL for tretinoin and 0.5 ng/mL for clindamycin. The lack of detecable drug levels in the plasma precluded determination of any meaningful toxicokinetic parameters, such as the time course of absorption or elimination or the occurrence of t_{max}. However, occasional measurable plasma levels of the actives suggest that the animals receiving dermal doses of ClinRA Gel were exposed systemically to low levels of clindamycin and/or tretinoin.

Conclusions

Local irritation was observed in all treatment groups with a slightly higher incidence and severity of erythema observed in the 125 mg formulation/kg/day ClinRA, ClinRA with tretinoin and ClinRA with clindamycin groups. No signs of systemic toxicity were noted at any dosage level tested. The dosage level of 125 mg formulation/kg/day (2750 $mg/m^2/day$) was considered a no-observed-adverse-effect level (NOAEL) for the 13-week administration of ClinRA in Hanford minipigs.

2.6.6.5 Carcinogenicity

The carcinogenicity study included in this submission, Dermal Carcinogenicity Study in Mice with Clindamycin Phosphate [redacted] Report No. 11484) was previously reviewed under [redacted] (SN008). No new carcinogenicity studies were included in this submission. b(4)

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: A dermal dose range-finding developmental toxicity study in New Zealand white rabbits with two weeks pre-treatment with ClinRA Gel

Key study findings: Based on the results of this study, dosage levels of 60, 180, and 600 mg/kg/day were selected for a definitive developmental toxicity study in New Zealand White rabbits with two weeks pretreatment with ClinRA Gel.
Laboratory Study no.: 3551.22
Sponsor Study no.: 7001-G2HP-04-02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: September 4, 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: ClinRA Gel, batch # LB-157
ClinRA Gel Vehicle, batch # LB-160

Methods

A total of 36 female New Zealand White rabbits ~ 7 months of age with body weights ranging from ~ 3.1 to 3.9 kg.were used in this study. The study design and dosage levels tested were as follows:

Group	# of Females	Material	ClinRA Gel Formulation				Tretinoin (0.025%) Dosage Level		Clindamycin (1%) Dosage Level	
			mL/kg/day	mg/kg/day	mg/m^2/day	mg/cm^2/day	mg/kg/day	mg/m^2/day	mg/kg/day	mg/m^2/day
1	6	ClinRA Gel Vehicle Gel	0.6	0	0	0	0	0	0	0
2	6	ClinRA Gel	0.06	60	660	2	0.015	0.165	0.6	6.6
3	6	ClinRA Gel	0.18	180	1980	2	0.045	0.495	1.8	19.8
4	6	ClinRA Gel	0.3	300	3300	2	0.075	0.825	3	33
5	6	ClinRA Gel	0.6	600	6600	2	0.150	1.65	6	66

Animals were dosed dermally once daily from 2 weeks prior to insemination until gestation day 18, inclusive at target dosage levels of 60, 180, 300, and 600 mg formulation/kg/day, and dosage volumes of 0.06, 0.18, 0.3, and 0.6 mL/kg, respectively. The targeted mg/cm^2/day dosage levels were based on application of a constant volume/unit skin area. Test article doses were increased by increasing the surface area treated. Following 2 weeks of treatment semen was collected from untreated stock male New Zealand White rabbits and used to inseminate the females. Detailed clinical observations were performed daily during the 2-week pre-insemination and gestation periods and also on the day of scheduled euthanasia. Dermal reactions were observed on specified pre-insemination and gestation days. The animals were weighed at specified intervals. Surviving females were euthanized on gestation day 29 by an intravenous injection of sodium pentobarbital via the marginal ear vein and subjected to cesarean section and gross necropsy examination. Fetuses were individually weighed and examined for external abnormalities. Findings were classified as malformations or developmental variations based on the severity of the anatomical change(s) and the extent of their potential for interference with organ and/or body function(s).

Results

Mortality: All females survived to scheduled cesarean section on gestation Day 29.

Clinical signs: No overt clinical signs of toxicity were noted during the study. Similar clinical signs were observed in the control and test article-treated groups during premating and gestation. Dermal findings were observed for female rabbits in each test article-treated group during premating and gestation. The severity of the findings appeared to be slightly greater in the 300 and 600 mg formulation/kg/day groups as compared to the 60 and 180 mg formulation/kg/day groups. The dermal findings included very slight to well-defined erythema, desquamation and test site staining in the 60 and 180 mg formulation/kg/day groups, and very slight to moderate to severe erythema, very slight edema, desquamation and test site staining in the 300 and 600 mg formulation/kg/day groups. A single incidence each of slight edema and focal and/or pinpoint areas of eschar on up to 10% of the test site was also observed in the 300 mg/kg/day group during the gestation period. Dermal findings in control animals were limited to one female rabbit with very slight erythema on three occasions during the gestation period.

Body weight: There were no dose-response patterns noted in mean body weights or body weight gain between the control and test article-treated groups.

Feed consumption: not monitored

Toxicokinetics: not monitored

Necropsy: A low incidence of findings was observed sporadically throughout the groups, but none of the findings were attributed to treatment with the test article.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.): There was a slight increase in the mean number of early resorptions in the 600 mg/kg/day group compared to controls. However, the mean value (0.7) remained within the historical control range for the test facility (0.2-0.9). No other remarkable differences were noted in the cesarean section parameters evaluated (i.e., number of corpora lutea, implantation sites, preimplantation loss, live fetuses, postimplantation loss, dead fetuses, early resorptions, late resorptions, and fetal body weights).

Offspring (malformations, variations, etc.): Two fetuses from two different litters in the 180 mg/kg/day group had external malformations. One fetus in the 180 mg/kg/day group had open eyelid, encephalomeningocele and omphalocele, and one other fetus in the 180 mg/kg/day group had gastroschisis. These findings were not considered test article related since they did not follow a consistent pattern or dose response. No other external malformations or developmental variations were observed for fetuses in the control or test article-treated groups.

Conclusions

Based on the results of this study, dosage levels of 60, 180, and 600 mg/kg/day were selected for the definitive developmental toxicity study in New Zealand White rabbits with two weeks pretreatment with ClinRA gel.

Study title: A dermal developmental toxicity study in New Zealand White rabbits with two weeks pre-treatment with ClinRA Gel

Key study findings: Based on the results of this study, a dosage level 600 mg/kg/day ClinRA Gel was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ClinRA Gel for 2 weeks prior to artificial insemination and continuing until gestation day 18, inclusive.

Laboratory Study no.: 3551.23
Sponsor Study no.: 7001-G2HP-06-02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: November 1, 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity:
Test Article A- ClinRA Gel, batch # LB-157, clin phos 103.6% LC, tretinoin 102.5% LC
Test Article B- ClinRA Gel with tretinoin 0.025% only, batch # LB-159, clin phos ND, tretinoin 101.8% LC
Test Article C- ClinRA Gel with clindamycin phosphate 1.2% only, batch # LB-158, clin phos 102.4% LC, tretinoin ND
ClinRA Vehicle Gel, batch # LB-160, clin phos ND, tretinoin ND

Methods

A total of 130 female New Zealand White rabbits ~ 5 months of age with body weights ranging from ~ 2.7 to 3.8 kg were used in this study. The study design and dosage levels tested were as follows:

Group	# of Females	Material	ClinRA Gel Formulation				Tretinoin (0.025%) Dosage Level		Clindamycin (1%) Dosage Level	
			mL/kg/day	mg/kg/day	$mg/m^2/day$	$mg/cm^2/day$	mg/kg/day	$mg/m^2/day$	mg/kg/day	$mg/m^2/day$
1	20	ClinRA Vehicle Gel	0.6	0	0	0	0	0	0	0
2	20	Test Article A	0.06	60	660	2	0.015	0.165	0.6	6.6
3	20	Test Article A	0.18	180	1980	2	0.045	0.495	1.8	19.8
4	20	Test Article A	0.6	600	6600	2	0.150	1.85	5	66
5	20	Test Article B	0.6	600	6600	2	0.150	1.85	0	0
6	20	Test Article C	0.6	600	6600	2	0	0	5	66

On the day prior to the first dose and as often as necessary thereafter, the fur was clipped from the entire dorsal area of the trunk of each female using an electric clipper. Animals were dosed dermally once daily from 2 weeks prior to insemination until gestation day 18, inclusive at target dosage levels of 60, 180, and 600 mg formulation/kg/day, and dosage volumes of 0.06, 0.18, and 0.6 mL/kg, respectively. The targeted mg/cm^2/day dosage levels were based on application of a constant volume/unit skin area. Following dosing, the test site was covered by an 8-ply gauze dressing secured using double-sided tape. A stockinette sleeve was fitted over the torso of each female to protect the site and reduce the possibility of unwanted oral exposure. The wrapping materials were removed on the following day and the test sites were gently wiped with gauze soaked in saline.

Following 2 weeks of treatment semen was collected from untreated stock male New Zealand White rabbits and used to inseminate the females. Semen from one male was used to inseminate an equal number of females in each group on each day.

General health/mortality checks were performed twice daily. Detailed clinical observations were performed daily during the 2-week pre-insemination and gestation periods and also on the day of scheduled euthanasia. Dermal reactions were observed pre-insemination days 0, 6, and 13, and on gestation days 6, 12, 18, 24, and 29. Individual body weights were recorded on pre-insemination days 0, 6, and 13 and on gestation days 1, 6, 9, 12, 15, 19, 24, and 29. Individual feed consumption was measured daily during the pre-insemination and gestation periods.

Surviving females were euthanized on gestation day 29 by an intravenous injection of sodium pentobarbital via the marginal ear vein and subjected to cesarean section and gross necropsy examination. Fetuses were individually weighed, sexed and examined for external, visceral and skeletal abnormalities. Findings were classified as malformations or developmental variations based on the severity of the anatomical change(s) and the extent of their potential for interference with organ and/or body function(s).

Toxicokinetic blood samples were obtained at 0 hour (prior to dosing), and at 1 hour, 4 hours, and 8 hours following dosing on pre-insemination day 10 and gestation day 18 consecutively from five females per group per time point. Blood samples were collected from the marginal ear vein into heparin-containing tubes and immediately chilled in a Kryorack. Plasma samples were obtained by centrifugation and stored in a tube containing ascorbic acid at ~ -70°C. Frozen plasma samples were subsequently shipped on dry ice to [redacted] for analysis. b(4)

Results

Mortality: All females survived to scheduled cesarean section on gestation day 29.

Pregnancy Status: The pregnancy rate was 85% in the control group, 600 mg/kg/day ClinRA Gel group, 600 mg/kg/day Tretinoin group and 600 mg/kg/day Clindamycin Phosphate group; 75% in the 60 mg/kg/day ClinRA Gel group; and 95% in the 180

mg/kg/day ClinRA Gel group. The pregnancy rates were all within the facility's historical control range of 70-100% for artificial insemination.

Clinical signs: No overt clinical signs of toxicity were noted during the study. Dermal findings were observed for females in each test article-treated group during pre-insemination and gestation. Findings were rated using the Draize test. During pre-insemination, the most commonly noted dermal observations not seen in control animals included erythema grade 2 and desquamation in all ClinRA Gel groups (groups 2-4) and the Tretinoin group (group 5). The incidence ranged from 13 to 20 animals per group with these findings. Dermal observations in the Clindamycin Phosphate group (group 6) were limited to four animals with grade 1 erythema. During gestation, some of the more commonly noted dermal observations not seen in control animals included erythema grade 2 and desquamation for the ClinRA Gel groups (groups 2-4) and the Tretinoin group (group 5) at an incidence of 20 animals per group. Additional dermal observations of erythema grades 3 and 4 occurred in the ClinRA Gel animals at a higher frequency in the higher dose groups. The Tretinoin group (group 5) showed similar effects to those seen in the high-dose ClinRA Gel group. However, the Clindamycin Phosphate group (group 6) did not appear to show any remarkable dermal observations during gestation.

Body weight: There were no remarkable differences in mean body weight or body weight change between the control and test article-treated groups.

Feed consumption: There were no remarkable differences in feed consumption between the control and test article-treated groups.

Toxicokinetics: Concentrations of clindamycin phosphate, tretinoin and its metabolites in the plasma samples collected, were generally not detectable or were below the lower limit of quantitation of 1.0 ng/mL for tretinoin and 0.5 ng/mL for clindamycin. There were measurable levels of clindamycin in some cases. These observations show that systemic exposure did occur.

Necropsy: No remarkable maternal gross necropsy findings were observed.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.): There was a slight increase in the mean number of postimplantation loss and mean number of early resorptions in the 600 mg/kg/day ClinRA Gel group and 600 mg/kg/day Clindamycin Phosphate group compared to controls. However, the mean values were within the facility's historical control range. No other remarkable differences were noted in the remaining cesarean section parameters evaluated, including mean number of corpora lutea, implantation sites, preimplantation loss, live fetuses, late resorptions and mean fetal body weight. Even though the mean fetal body weight for the 600 mg/kg/day ClinRA Gel group was slightly lower than the control group (5.4%), it was still within the historical control range (39.4-51.2). The mean fetal weights for the remaining test article groups were comparable to the control.

Offspring (malformations, variations, etc.): No statistically significant differences in fetal external, visceral and skeletal malformations or variations were noted in the test article-related groups compared to controls. A low incidence of malformations and variations known to occur spontaneously was observed throughout the groups, including controls, but there did not appear to be an apparent relationship to dose.

Conclusions

Based on the results of this study, a dosage level of 600 mg/kg/day ClinRA Gel was considered to be the no-observed-adverse-effect level (NOAEL) for systemic maternal and developmental toxicity following dermal administration of ClinRA Gel for 2 weeks prior to artificial insemination and continuing until gestation day 18, inclusive.

2.6.6.7 Local tolerance

No new local tolerance studies were included in this submission.

2.6.6.8 Special toxicology studies

Study title: FHSA Primary Skin Irritation

Key study findings: Under the conditions of this test, the test article was not a primary irritant as defined in the Federal Hazardous Substances Act (FHSA) regulation (16 CFR 1500.3).

Sponsor Study no.: 7001-G2HP-01-02
Laboratory Study no.: X2G176G
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: July 12, 2002
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: ClinRA Gel, LB-157

Methods

Six young adult New Zealand White rabbits (males) each received a single application of 0.5 mL of the undiluted test formulation, ClinRA Gel to intact and abraded skin. The abraded skin site was prepared by scoring the skin with the point of a 25 gauge needle. This was done in a way so as to penetrate the stratum corneum, but not the dermis. Skin sites were covered with a 1 inch gauze patch and the trunk of each animal was wrapped with a 6 inch bandage to preclude oral ingestion. The trunk of each animal was then wrapped with an elastic bandage and secured with staples so that complete occlusion was obtained. Test sites were uncovered after 24 hours of exposure. Residual test material was removed by gently swabbing with lukewarm water. The test sites were observed and scored for erythema and edema (using the Draize rating system) 24 and 72 hours after

dosing. Based on the scores, a mean Primary Irritation score (MPI) was calculated and the test material was classified for skin irritation potential according to FHSA guidelines.

Results:
The MPI score was calculated to be 0.5 and based on the descriptive rating, the formulation is a mild irritant (MPI 0-2). As defined in the FHSA regulations, a primary irritant is a substance that results in an empirical score of ≥ 5 when tested by this method. Therefore ClinRA Gel is not a primary skin irritant.

Study title: FHSA Primary eye irritation

Key study findings: Under the conditions of this test, the test article did not cause a positive irritation response in the eyes of six rabbits and is not considered a primary eye irritant as defined in 16 CFR Part 1500.42

Sponsor Study no.: 7001-G2HP-03-02
Laboratory Study no.: X2G285G
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: July 25, 2002
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: ClinRA Gel, LB-157

Methods
Six young adult New Zealand White rabbits (3 males and 3 females) each received a single instillation of 0.1 mL of the undiluted test article into the right eye. The other eye was left untreated to serve as a control. The animal's eyelid was held closed for ~ 1 second to prevent loss of the test article. Both eyes were rinsed with saline after 24 hours. The eyes were examined by gross observation for evidence of irritation at 24, 48, and 72 hours following administration. At each observation period, the eyes were examined for evidence of corneal ulceration or opacity, inflammation of the iris, or redness and chemosis of the conjunctivae. Observations were given scores according to the Draize rating system.

Results:
There was no evidence or irritation or corrosion to the eyes of any animal. Therefore the formulation is not a primary eye irritant as defined in 16 CFR Part 1500.42.

Study title: Maximization sensitization test (ISO)

Key study findings: Based on the results of this test, the test article ClinRA Gel, is not a contact sensitizer and did not induce an allergic reaction in Hartley albino guinea pigs. According to the International Organization for Standardization (ISO) criteria for this test, the sensitization potential of the test article was classified as grade 1 (no different than control) (ISO 10993-10, 1995).

Laboratory Study no.: X2G177G
Sponsor Study no.: 7001 G2HP-02-02
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: July 12, 2002
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: ClinRA Gel, lot# LB-157

Methods

Thirty-nine young adult Hartley guinea pigs were used in this test, including 12 test group animals (12 females), 6 negative (vehicle) control animals (6 females), 6 positive control animals (3 males and 3 females), and 6 naïve positive control animals (3 males and 3 females). Nine animals (sex not specified) were used in preliminary dosing screens. The positive control test was performed as a historical study ([redacted] tudy # X2B048G) conducted in February and March 2002. Sterile Water for Injection (WFI) was the negative control. The positive control was 1-chloro-2,4-dinitrobenzene (DNCB). The guinea pigs were initially exposed to the test formulation and the control solutions in an induction phase lasting 9 days. In this phase, the test article and controls were first injected intradermally (ID). For the ID injections, the test article was diluted in a 5% (vol/vol) solution with WFI. The 5% solution was injected directly as well as emulsified with Freund's Complete Adjuvant (FCA). The control group animals received ID injections of WFI (negative control) and DCNB (positive control) prepared in a similar manner, used directly or emulsified in FCA. Seven days after the ID injections, the undiluted test formulation, WFI and positive control solution were administered topically over the same area in which the ID injections were given in their respective groups. The topical exposure lasted 48 hours. b(4)

Fourteen days after the topical administration, the animals were challenged. For the challenge phase, the undiluted test formulation and control solutions were administered topically to untreated sites on the animals' flanks, and remained on the animals for 24 hours. The dosing sites were scored for erythema and edema 24, 48, and 72 hours after removal of the chambers. Based on the erythema and edema scores observed, the test article was classified as to its allergic potential.

Results:

Only one (#78348) of twelve test group animals (8%) received scores greater than those of the negative control animals, with a score of 1 (slight erythema) at the 24 and 72 hour observations. The negative control group had no reactions. All positive control animals exhibited a strong sensitization response to the challenge dose compared to those of the naïve positive control. This establishes that the treatment conditions were able to induce a response from a known sensitizer.

Conclusions:

Based on the results of this test, the test article ClinRA Gel, is not a contact sensitizer and did not induce an allergic reaction in Hartley albino guinea pigs. According to the ISO criteria for this test, the sensitization potential of the test article was classified as grade 1 (no different than control) (ISO 10993-10, 1995).

2.6.6.9 Discussion and Conclusions

A dosage level of 125 mg ClinRA Gel/kg/day, the highest dose tested, was considered to be the NOAEL following 13 weeks of topical application in Hanford minipigs. A dosage level of 600 mg ClinRA Gel/kg/day, the highest dose tested, was considered to be the NOAEL for systemic maternal and developmental toxicity following dermal application for 2 weeks prior to artificial insemination and continuing until gestation day 18 in New Zealand white rabbits. ClinRA Gel was not considered to be a primary skin irritant or a primary eye irritant in rabbits. ClinRA Gel was not a sensitizer when tested in the guinea pig maximization test. There does not appear to be any reason to expect the proposed combination of clindamycin phosphate and tretinoin to have greater toxicity than other previously approved topical formulations of either clindamycin phosphate or tretinoin.

2.6.6.9 Tables and Figures

This section is not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

This section is not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The inactive ingredients in ClinRA Gel are all used in other approved topical drug products. It is not clear if Carbomer 981 is used in an approved product at a concentration as high as 0.75%. However, other closely related carbomers are used at higher concentrations in approved products. In addition, this carbomer was present in the test articles used in the nonclinical studies conducted with ClinRA Gel. Consequently, the use of Carbomer 981 does not raise safety concerns. Based on the nonclinical data available for clindamycin phosphate and tretinoin, NDA 21-739 is approvable from a pharmacological/toxicological perspective.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 21-739, at this time.

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

References:

Allen JG, Bloxham DP. The pharmacology and pharmacokinetics of the retinoids. *Pharmacol Ther* 1989;40(1):1-27.

Barua AB, Olson JA. Percutaneous absorption, excretion and metabolism of all-*trans*-retinoyl β-glucuronide and of all-*trans*-retinoic acid in the rat. *Skin Pharmacol* 1996; 9(1):17-26.

Bollert JA, Gray JE, Highstrete JD, Moran J, Purmalis BP, Weaver RN. Teratogenicity and neonatl toxicity of clindamycin 2-phosphate in laboratory animals. *Toxicol Appl Pharmacol* 1974 Feb;27(2):322-9.

Budroe JD, Schol HM, Shaddock JG, Casciano DA. Inhibition of 7,12-dimethylbenz[a]anthracene-induced genotoxicity in Chinese hamster ovary cells by retinol and retinoic acid. *Carcinogenesis* 1988 Jul;9(7):1307-11.

Christian MS, Mitala JJ, Powers WJ Jr, McKenzie BE, Latriano L. A developmental toxicity study of tretinoin emollient cream (Renova) applied topically to New Zealand white rabbits. *J Am Acad Dermatol* 1997 Mar;36(3 Pt 2):S67-76.

Chytil F. Retinoic acid: Biochemistry and metabolism. *J Am Acad Dermatol* 1986; 15(4, pt 2):741-747.

Connor MJ, Lowe NJ, Breeding JH, Chalet M. Inhibition of ultraviolet-B skin carcinogenesis by all-*trans*-retinoic acid rgimens that inhibit ornithin Decarboxylase induction. *Cancer Research* 1983; 43:171-174.

Eller MG, Smith RB, Phillips JP. Absorption kinetics of topical clindamycin preparations. *Biopharm Drug Dispos* 1989 Sep-Oct; 10(5):505-12.

Epstein JH, Grekin DA. Inhibition of ultraviolet-induced carcinogenesis by all-*trans*-retinoic acid. *J Investigat Dermatol* 1981;76:178-180.

Forbes PD, Urbach F, Davies, RE. Enhancement of experimental photocarcinogenesis by topical retinoic acid. *Cancer Let* 1979;7:85-90.

Forbes PD. Photocarcinogenesis: An overview. *J Investigat Dermatol* 1981; 77:139-143.

Franz TJ, Lehman PA. Systemic absorption of retinoic acid. *J Cut & Ocular Toxicol* 1990; **8**(4):517-524.

Gray JE, Stern K, Weaver R, *et al.* Percutaneous absorption of clindamycin in the pig and the rat. *Int J Dermatol* 1983; **22**(5):314-317.

Gray JE, Weaver RN, Bollert JA, Feenstra ES. The oral toxicity of clindamycin in laboratory animals. *Toxicol Appl Pharmacol* 1972; **21**:516-531.

Halliday GM, Robertson BO, Barnetson RSC. Topical retinoic acid enhances, and a dark tan protects, from subedemal solar-simulated photocarcinogenesis. *J Invest Dermatol* 2000; 114:923-927.

Hand WL, Corwin RW, Steinberg TH, Grossman GD. Uptake of antibiotics by human alveolar macrophages. *Am Rev Respir Dis* 1984; **129**(6):933-937.

Hand WL, King-Thompson NL. Uptake of antibiotics by human polymorphonuclear leukocyte cytoplasts. *Antimicrob Agents Chemother* 1990a; **34**(6):1189-1193.

Hand WL, Hand DL, King-Thompson NL. Antibiotic inhibition of the respiratory burst response in human polymorphonuclear leukocyctes. *Antimicrob Agents Chemother* 1990b; **34**:863-870.

Herold M, Cahn J, Gomont P. Toxciology of vitamin A acid. *Acta Derm Venereol Suppl (Stockh)*. 1975 Jan 27-29;74:29-32.

Holson RR, Cogan JE, Adams J. Gestational retinoic acid exposure in the rat: effects of sex, strain and exposure period. *Neurotoxicol Teratol* 2001 Mar-Apr;23(2):147-56.

Idres N, Benoit G, Flexor MA, Lanotte M, Chabot GG. Granulocytic differentiation of human NB4 promyelocytic leukemia cells induced by all-*trans*-retinoic acid metabolites. *Cancer Res* 2001;61(2):700-705.

Kamm JJ. Toxicology, carcinogenicity, and teratogenicity of some orally administered retinoids. *J Am Acad Dermatol* 1982 Apr;6(4 Pt 2 Suppl):652-9.

Kligman LH. Retinoic acid and photocarcinogenesis – a controversy. Photodermatol 1987;4:88-101.

Kligman LH, Kligman AM. Lack of enhancement of experimental photocarcinogenesis by topical retinoic acid. *Arch Dermatol Res* 1981;270(4):453-462.

Kligman LH, Mezick JA, Capetola RJ, Thorne G. Lifetime topical application of tretinoin to hairless mice. *Acta Derm Venereol (Stockholm)* 1992; 72:418-422.

Kochhar DM, Christian MS. Tretinoin: A review of the nonclinical developmental toxicology experience. *J Am Acad Dermatol* 1997; **36**(3, pt2):S47-S59.

Kraft JC, Kochhar DM, Scott WJ, Nau H. Low teratogenicity of 13-*cis*-retinoic acid (isotretinoin) in the mouse corresponds to low embryo concentrations during organogenesis: comparison to the all-*trans* isomer. *Toxicol Appl Pharmacol* 1987; **87**(3):474-482.

Kraft JC, Lofberg B, Chahoud I, Bochert G, Nau H. Teratogenicity and placental transfer of all-*trans*-, 13-cis-, 4-oxo all-*trans*-, and 4-oxo-14-*cis*-retinoic acid after administration of a low oral dose during organogenesis in mice. *Toxicol Appl Pharmacol* 1989; **100**(1):162-176.

Kraft JC, Slikker W, Bailey JR *et al.* Plasma pharmacokinetics and metabolism of 13-*cis* and all-*trans* retinoic acid in the cynomologus monkey and the identification of 13-*cis* and all-*trans*-retinoyl-β-glucuronides: a comparison to one human case study with isotretinoin. *Drug Metab Dispos* 1991; 19:314-324.

Kretzschmar R, Leuschner F. Biosynthesis and metabolism of retinoic acid. *Acta Derm Venereol Suppl (Stockh)*. 1975 Jan 27-29;25-8.

Kurtz PJ, Emmerling DC, Donofrio DJ. Subchronic toxicity of all-*trans*-retinoic acid and retinylidene dimedone in Sprague-dawley rats. *Toxicology* 1984 Mar;30(2):115-24.

Lindamood C 3rd, Cope FO, Dillehay DL, Everson MP, Giles HD, Lamon EW, McCarthy DJ, Sartin JL, Hill DL. Pharmacological and toxicological properties of arotinoids SMR-2 and SMR-6 in mice. *Fundam Appl Toxicol* 1990 Jan;14(1):15-29.

Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985 Jan-Feb; 10(1):38-62.

Lusk RH, Fekety R, Silva J, Browne RA, Ringler DH, Abrams GD. Clindamycin-induced enterocolitis in hamsters. *J Infect Dis* 1978 Apr;137(4):464-75.

Marill J, Cresteil T, Lanotte M, Chabot GG. Identification of human cytochrome P450s involved in the formation of all-*trans*-retinoic acid principal metabolites. *Mol Pharmacol* 2000; **58**(6):1341-1348.

Marill J, Capron CC, Idres N, Chabot GG. Human cytochrome P450s involved in the metabolism of 9-*cis*- and 13-*trans*-retinoic acids. *Biochem Pharmacol* 2002; **63**(5):933-943.

Nishimura T, Iwase T, Hashimoto Y, Tanimura T. Evaluation of a core battery of tests for detecting behavioral dysfunction of rat offspring induced by retinoic acid: Collaborative work II of the Japanese behavioral teratology committee. *Congenital Anomalies* 2001;41:156-168.

Nolen GA. The effects of prenatal retinoic acid on the viability and behavior of the offspring. *Neurobehav Toxicol Teratol* 1986 Nov-Dec;8(6):643-54.

Seegmiller RE, Ford WH, Carter MW, Mitala JJ, Powers WJ Jr. A developmental toxicity study of tretinoin administered topically and orally to pregnant Wistar. *J Am Acad Dermatol* 1997 Mar;36(3 Pt 2):S60-6.

Snyder RD, Green JW. A review of the genotoxicity of marketed pharmaceuticals. *Mutat Res* 2001;488:151-169.

Sun FF, Hsi RSP. Metabolism of clindamycin I: Absorption and excretion of clindamycin in rat and dog. *J Pharm Sci* 1973a; **62**(8):1265-1269.

Sun FF. Metabolism of clindamycin II: Urinary excretion products of clindamycin in rat and dog. *J Pharm Sci* 1973b; **62**(10):1657-1662.

Tsubura Y, Yamamoto H. (Japanese with English summary). Effect of long-term dermal application of retinoic acid on mice with special reference to the solvent and the application interval. *J Nara Med Ass* 1979; 30:55-67.

Tžimas G, Burgin H, Collins MD, Hummler H, Nau H. The high sensitivity of the rabbit to the teratogenic effects of 13-*cis*-retinoic acid (isotretinoin) is a consequence of prolonged exposure of the embryo to 13-*cis*-retinoic acid and 13-*cis*-4-oxo-retinoic acid, and not of isomerization to all-*trans*-retinoic acid. *Arch Toxicol* 1994; 68:119-128.

Voisin C, Carre Ph, Piva F, Wallaert B. Antibiotics and alveolar macrophages: a review (in French). *Path Biol* 1987; 35(10):1412-1417.

White JA, Beckett-Jones B, Guo YD, Dilworth FJ, Bonasoro J, Jones G, Petkovich M. cDNA Cloning of human retinoic acid-metabolizing enzyme (hP450RA1) identifies a novel family of cytochromes P450 (CYP26). *J Biol Chem* 1997; **272** (30):18538-18541.

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/s/

Jill Merrill
11/23/04 11:04:25 AM
PHARMACOLOGIST

PT review of NDA

Paul Brown
11/23/04 03:46:19 PM
PHARMACOLOGIST

Division of Dermatologic and Dental Drug Products (HFD-540)
Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date:	3-31-04
Reviewer:	Jill Merrill
NDA Number:	21-739
Drug Name:	ClinRa (clindamycin 1%, tretinoin 0.025%) Gel
CAS Number:	Clindamycin phosphate: 24729-96-2 Tretinoin: 302-79-4
Drug Class:	Clindamycin phosphate: lincosamide antibiotic Tretinoin: retinoid
Indication:	Acne vulgaris
Route of Administration:	Topical
Date CDER Received:	2-9-04
User Fee Date:	12-9-04
Date of Draft Review:	8-9-04
Sponsor:	Dow Pharmaceutical Sciences, Petaluma, CA

Fileability:

On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? YES

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? YES

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? YES

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? YES

This NDA for ClinRa (clindamycin 1%, tretinoin 0.025%) Gel is being submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act. It refers to published literature for much of the nonclinical information normally required to support an NDA. The following list includes the pivotal studies, either sponsor-conducted studies or those from the open literature.

ClinRa Gel

Single-dose rodent:
Rat, oral (sponsor)
Multiple-dose non-rodent:
Minipig, dermal, 13-week with 4-week recovery (sponsor)
Reproductive and developmental toxicity:
Embryo-fetal development:
Rabbit, dermal range-finding, (sponsor)
Rabbit, dermal, (sponsor)
Special toxicity studies:
Rabbit, dermal irritation (sponsor)
Rabbit, ocular irritation (sponsor)
Guinea pig, skin sensitization (sponsor)

Clindamycin
Teratogenicity
Rodents (literature)
Genotoxicity
Ames test (literature)
In vivo cytogenetics (literature)
Carcinogenicity:
Mouse, dermal, 1% clindamycin phosphate gel (sponsor by right-of-reference)

Tretinoin
Fertility, peri- and postnatal
Rat (literature)
Teratogenicity
Rodent and non-rodent (literature)
Genotoxicity
Ames test (literature)
In vitro SCE (literature)
In vitro chromosome aberration in CHO (literature)
Carcinogenicity
Mouse, dermal, ≤0.1% tretinoin (literature)
Photocarcinogenicity
Mouse, dermal, ≤0.3% tretinoin (literature)

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? NA

(6) Are the proposed labeling sections relative to pharm/tox appropriate

(including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? YES

However, some sections may need to be updated at the NDA review according to current standards.

(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? YES

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? YES

Some of the studies were conducted by routes other than topical but this is acceptable.

(9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? YES

Sponsor states: All nonclinical toxicology studies were conducted in accordance with Part 58 of the CFR.

(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? N/A

(11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? YES

Sponsor states: All pharmacological/toxicological studies conducted in support of ClinRa Gel have been performed using acceptable, state-of-the-art protocols reflective of Agency animal welfare concerns.

(12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. YES

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: NO

(14) Issues that should not be conveyed to the Sponsor: N/A

_____
Pharmacology Reviewer

_____
Pharmacology Supervisor

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

/s/

Jill Merrill
3/31/04 02:00:07 PM
PHARMACOLOGIST

please find attached the filing letter

Paul Brown
4/1/04 11:51:01 AM
PHARMACOLOGIST