CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208079Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 208079
Supporting document/s:	SDN1, SDN5
Applicant's letter date:	04/06/2015, 08/14/2015
CDER stamp date:	04/06/2015, 08/14/2015
Product:	Sernivo (betamethasone) dipropionate spray, 0.05%
Indication:	Topical treatment of moderate (b) (4) plaque psoriasis
Applicant:	Promius Pharma, LLC
Review Division:	DDDP
Reviewer:	Jill C Merrill, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Kendall Marcus, MD
Project Manager:	Strother Dixon

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The sponsor has developed a novel topical formulation of betamethasone dipropionate, 0.05% (Sernivo Spray) as a topical treatment for moderate (b) (4) plaque psoriasis. Betamethasone dipropionate is a fluorinated corticosteroid that has been FDA approved for the treatment of psoriasis, atopic dermatitis and other inflammatory skin diseases since 1975. The sponsor is seeking a 505(b)(2) regulatory pathway with Diprolene® Lotion (augmented), NDA 19716 (Merck Sharp Dohme, approved 08/01/1988) as the listed drug. The Agency's Clinical Pharmacology reviewer agrees that the sponsor has generated an adequate clinical bridge to the listed drug. Thus a 505(b)(2) regulatory submission is appropriate.

1.2 Brief Discussion of Nonclinical Findings

The sponsor is relying on FDA's findings of safety for Diprolene® Lotion (NDA 19716, approved 08/01/1988) and the published literature to support the systemic safety of Sernivo Spray, 0.05%. Betamethasone was negative in bacterial and mammalian mutagenicity assays, positive in the in vitro chromosomal aberration assay, and equivocal in the in vivo mouse micronucleus assay. It caused a dose-related increase in fetal resorptions in rabbits and mice. Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg.

The sponsor conducted repeat-dermal toxicity studies with betamethasone dipropionate in both rodents and nonrodents. In a 13-week toxicity study in rats, topical administration of betamethasone dipropionate at dose concentrations of 0.05% and 0.1% (which corresponds to dose levels up to up to 0.5 mg/kg/day in males and 0.25 mg/kg/day in females) resulted in reduced body weight gain and adrenal atrophy consistent with the reported toxicological effects of synthetic corticosteroids. Based on the test article-induced immunosuppression the sponsor was granted a waiver for conduct of a 2-year dermal carcinogenicity study.

A 28-day dermal toxicity study was conducted in minipigs with daily topical administration of 0.05% and 0.1% betamethasone dipropionate (providing dose levels up to 1.5 mg/kg/day in males and 1.0 mg/kg/day in females). Although this study was terminated early due to severe dermal irritation attributed to the vehicle, clinical pathology, organ weight and microscopic changes in the treated animals were consistent with the anti-inflammatory and immunosuppressive effects of corticosteroids. An additional dermal toxicity study in an alternate nonrodent model is not considered necessary.

Betamethasone dipropionate, 0.05% spray did not elicit a delayed contact hypersensitivity response in guinea pigs nor was it a dermal or ocular irritant when tested in rabbits.

1.3 Recommendations

1.3.1 Approvability

Sernivo Spray, 0.05% is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The sponsor has elected to keep the label in the original non-PLLR format (SDN5). Promius Pharma, LLC commits to change to the full PLLR format before June 30, 2019.

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Sernivo™ label text. A clean copy of these revised labeling sections is provided in Appendix #1.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

SERNIVO Spray is a (b) (4) corticosteroid indicated for the treatment of moderate plaque psoriasis in patients 18 years of age or older (1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

(b) (4) Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SERNIVO Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of SERNIVO Spray in psoriasis is unknown.

NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of (b) (4)-betamethasone dipropionate.

In a 90-day repeat-dose toxicity study in rats, topical administration of betamethasone dipropionate spray formulation at dose concentrations of 0.05% and 0.1% (providing dose levels up to 0.5 mg/kg/day in males and 0.25 mg/kg/day in females) resulted in a toxicity profile consistent with long-term exposure to corticosteroids including reduced body weight gain, adrenal atrophy, and histological changes in bone marrow, thymus and spleen indicative of severe immune suppression. A no observable adverse effect level (NOAEL) could not be determined in this study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay.

Studies in rabbits, mice, and rats using intramuscular doses up to 1, 33, and 2 mg/kg, respectively, resulted in dose-related increases in fetal resorptions in rabbits and mice.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 5593-20-4

Generic Name: betamethasone dipropionate

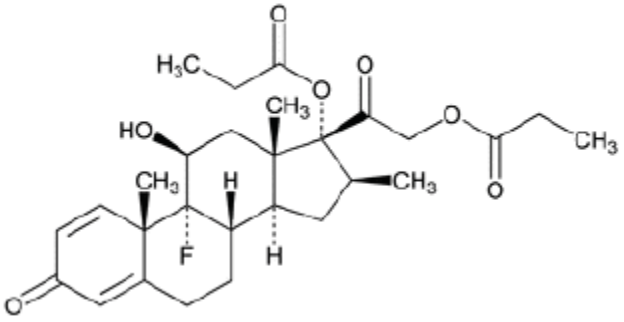
Code Name: DFD-01

Chemical Name: 9-fluoro-11(β),17,21-trihydroxy-16(β)-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate

Molecular Formula/Molecular Weight $C_{28}H_{37}FO_7$ / 504.6

Structure

Structural Formula



Pharmacologic Class: corticosteroid

2.2 Relevant INDs, NDAs, and MFs

IND 104853, submitted 07-04-2010

NDA 19716, Diprolene® Lotion (augmented), Merck Sharp and Dohme Corp., approved 08-01-1988

MF (b) (4) betamethasone dipropionate

2.3 Drug Formulation

The quantitative formulation for Sernivo Spray, 0.05% is provided in the following table.

Ingredient	% w/w
Betamethasone dipropionate, USP/EP	0.0643
Sorbitan monostearate, USP/NF	(b) (4)
Polyoxyl 20 cetostearyl ether, USP/NF	
Cetostearyl alcohol USP/NF	
Mineral oil, USP	
Oleyl alcohol, USP/NF	
Propylparaben, USP/NF	
Methylparaben, USP/NF	
Butylated hydroxytoluene, USP/NF	
Hydroxyethyl cellulose, USP	
Purified water, USP	

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

SERNIVO Spray is indicated for up to 4 weeks of twice daily treatment of psoriasis in patients 18 years of age or older. Discontinue treatment when control is achieved. Treatment beyond 4 weeks is not recommended.

2.7 Regulatory Background

The sponsor had a pre-IND meeting with the Division (June 17, 2009) and is seeking a 505(b)(2) regulatory pathway with Diprolene® Lotion (augmented), NDA 19716 (approved 08/01/1988) as the listed drug.

3 Studies Submitted

3.1 Studies Reviewed

None.

3.2 Studies Not Reviewed

The following studies have been previously reviewed under IND 104853. Summaries of pivotal studies are provided in the corresponding section of this document.

Toxicology

Betamethasone dipropionate spray (0.05% w/w and 0.1% w/w): A 28-day repeated dose dermal toxicity study in Sprague Dawley rats (study # G8381)

Betamethasone dipropionate spray 0.05% and 0.1% w/w: A 13-week dermal carcinogenicity dose range-finding study in rats (study # 13-2355)

Betamethasone dipropionate spray 0.05% and 0.1% w/w: A 28-day dermal toxicity study in minipigs (study # 13-3140)

Special Toxicology Studies

Delayed contact dermal sensitization test in guinea pigs – Buehler method (study # 1160-05)

Acute dermal irritation/corrosion in rabbits (study # 2130-05)

Eye irritation/corrosion in rabbits (study # 2200-04)

Placebo for betamethasone dipropionate spray: A 14-day comparative dermal irritation study in minipig (study # 13-3182)

Dermal phototoxicity screening in mice (study # 13-C-9104)

3.3 Previous Reviews Referenced

IND 104853, pharmacology/toxicology reviews

4 Pharmacology

4.1 Primary Pharmacology

Corticosteroids play a major role in cellular signaling, immune function, inflammation, and protein regulation. The precise mechanism of action of betamethasone dipropionate in psoriasis is unknown.

4.2 Secondary Pharmacology

The most significant secondary activity of corticosteroids in clinical use is suppression of the hypothalmic-pituitary-adrenal axis. Adrenocorticotropic hormone suppression is mediated by transrepression (Schacke *et al.*, 2004). The activated receptor also binds to DNA to induce transcription (transactivation). Secondary effects due to transactivation include increase in blood glucose, spleen involution, and skin atrophy.

4.3 Safety Pharmacology

Not provided.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed through normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Once absorbed through the skin, topical corticosteroids enter pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees, are metabolized primarily in the liver, and excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Plasma concentrations of betamethasone dipropionate, betamethasone-17-propionate, and betamethasone were measured at baseline, and before and after the last dose (1, 3, and 6 hours) in an HPA axis suppression trial in 75 subjects with psoriasis. The majority of subjects had no measurable plasma concentration (<5.00 pg/mL) of betamethasone dipropionate, while the metabolites, betamethasone-17-propionate and

betamethasone, were detected in the majority of subjects (see Table 2 taken directly from the label). There was high variability in the data but there was a trend toward higher systemic exposure at day 15 and lower systemic exposure at day 29.

Table 1: Mean (±SD) Maximum Plasma Concentrations (pg/mL) of Betamethasone Dipropionate Metabolites after 15 or 29 Days of Treatment with SERNIVO Spray

Analyte (pg/mL)	SERNIVO Spray *b.i.d.* (15 days)	SERNIVO Spray *b.i.d.* (29 days)
Betamethasone-17-propionate	120 ± 127	63.9 ± 52.6
Betamethasone	119 ± 176	57.6 ± 55.9

5.2 Toxicokinetics

Toxicokinetic data is included in the repeat-dose dermal rat study summarized under Section 6.2.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were included in the NDA submission.

6.2 Repeat-Dose Toxicity

Title: Betamethasone dipropionate spray 0.05% and 0.1% w/w: A 13-week dermal carcinogenicity dose range-finding study in rats

In a 90-day repeat-dose toxicity study in rats topical administration of betamethasone dipropionate at dose concentrations of 0.05% and 0.1% (which corresponds to doses from 0.125 to 0.5 mg/kg/day in males and from 0.0625 to 0.25 mg/kg/day in females) resulted in a toxicity profile consistent with long-term exposure to corticosteroids including reduced body weight gain, adrenal atrophy, decreased leukocyte count, and decreased cellularity in bone marrow, thymus and spleen. The observed effects were consistent with the reported toxicological effects of synthetic corticosteroids and reflected immunosuppression. A no observable adverse effect level (NOAEL) could not be determined in this study.

Maximum mean plasma concentrations (C_{max}) of betamethasone and the areas under the mean plasma betamethasone concentration-time curves estimated up to 24 hours postdose (AUC_{0-24}) on Day 1 and Day 90 are summarized below:

Dose level (mg/kg)		C_{max} (ng/mL)				AUC_{0-24} (ng.h/mL)			
		Day 1		Day 90		Day 1		Day 90	
Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
0.125	0.0625	BLQ	4.75	0.794	3.73	-	45.4	3.92	36.5
0.25	0.125	0.374[a]	3.43	1.62	6.69	2.87[a]	27.5	14.2	68.3
0.5	0.25	0.516	9.08	1.44	9.76	5.94	95.1	17.4	122

[a] Less than 3 consecutive quantifiable mean plasma concentrations, data retained as 15/27 samples were quantifiable

The systemic exposure of betamethasone appeared to be characterized by non-linear (dose-dependent) kinetics for C_{max}, whereas the extent (AUC_{0-24}) appeared to be characterized by dose-independent (linear) kinetics over the same dose range except in females on Day 1 which was less than proportionate. In addition, the study also provided evidence that the systemic exposure of female rats to betamethasone was on average 16-fold higher than in males when administered at the same dose levels, and that there was some accumulation after repeated dermal administration in both sexes although this tended to be greater in males than in females.

Title: Betamethasone dipropionate spray 0.05% and 0.1% w/w: A 28-day dermal toxicity study in minipigs

The sponsor conducted a 28-day dermal toxicity study in minipigs with daily topical administration of 0.05% and 0.1% betamethasone dipropionate (males: 0, 0.5, 0.75, 1.5 mg/kg/day; Females: 0, 0.25, 0.50, 1.0 mg/kg/day). Severe, unexpected dermal irritation, inversely related to the increasing dose of betamethasone dipropionate, was attributed to the vehicle and resulted in early termination of this study. Although analysis of the vehicle revealed microbial contamination, a subsequent follow-up study indicated microbial contamination had no apparent impact on the incidence or severity of dermal irritation. Although this study was terminated early, clinical pathology, organ weight and microscopic pathology changes in the betamethasone dipropionate-treated animals were consistent with the anti-inflammatory and immunosuppressive effects of this corticosteroid. An additional dermal toxicity study in an alternate nonrodent model is not considered necessary.

7 Genetic Toxicology

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the in vitro human lymphocyte chromosome aberration assay, and equivocal in the in vivo mouse bone marrow micronucleus assay.

8 Carcinogenicity

Data from a 13-week rat dermal study (13-2355) showed that betamethasone dipropionate caused immunosuppression as well as significant toxicity in multiple organ systems after only 13 weeks of daily dermal dosing. Based on the extent of test article-induced immunosuppression noted in the 13-week toxicity study, conduct of a 2-year dermal carcinogenicity study is not practical. Accordingly, the sponsor was granted a waiver request for conduct of the dermal carcinogenicity study. The results of the 13-week rat study should be incorporated into Section 13.1 of the Sernivo Spray label.

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

9 Reproductive and Developmental Toxicology

The sponsor anticipates a 505(b)(2) NDA approval process with Diprolene® Lotion (augmented), NDA 19716 (approved 08/01/1988) as the listed drug. The following information appears in the corresponding sections of the label for Diprolene® Lotion.

9.1 Fertility and Early Embryonic Development

Studies in rabbits, mice and rats using intramuscular doses of up to 1, 33, and 2 mg/kg, respectively, resulted in dose-related increases in fetal resorptions in rabbits and mice.

9.2 Embryonic Fetal Development

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

10 Special Toxicology Studies

The sponsor's special toxicology studies were previously reviewed under IND 104853. Conclusions are provided below:

Betamethasone dipropionate spray, 0.05% was found not to be classified as an eye irritant when tested in rabbits (2200-04).

Betamethasone dipropionate spray, 0.05% was not a dermal irritant in rabbits after a 4-hour application (2130-05).

Betamethasone dipropionate 0.05% spray did not elicit a delayed contact hypersensitivity response in guinea pigs (1160-05).

Neither betamethasone dipropionate spray, 0.05% nor its placebo are phototoxic when tested in mice (13-C-9104).

11 Integrated Summary and Safety Evaluation

Under this 505(b)(2) application the sponsor is relying on the agency's findings of systemic safety for Diprolene® Lotion, the listed drug. The sponsor conducted topical repeat-dose toxicity studies with betamethasone dipropionate in both rodents and nonrodents. In both cases betamethasone dipropionate produced effects consistent with the known effects of corticosteroids.

Betamethasone dipropionate spray, 0.05% for the treatment of plaque psoriasis is approvable from a Pharmacology/Toxicology perspective.

12 Appendix/Attachments

Recommended Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

SERNIVO Spray is a corticosteroid indicated for the treatment of moderate plaque psoriasis in patients 18 years of age or older (1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. SERNIVO Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephalocele, and cleft palate.

CLINICAL PHARMACOLOGY
12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of SERNIVO Spray in psoriasis is unknown.

NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a 90-day repeat-dose toxicity study in rats, topical administration of betamethasone dipropionate spray formulation at dose concentrations of 0.05% and 0.1% (providing dose levels up to 0.5 mg/kg/day in males and 0.25 mg/kg/day in females) resulted in a toxicity profile consistent with long-term exposure to corticosteroids including reduced body weight gain, adrenal atrophy, and histological changes in bone marrow, thymus and spleen indicative of severe immune suppression. A no observable adverse effect level (NOAEL) could not be determined in this study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Betamethasone was negative in the bacterial mutagenicity assay (*Salmonella typhimurium* and *Escherichia coli*), and in the mammalian cell mutagenicity assay (CHO/HGPRT). It was positive in the *in vitro* human lymphocyte chromosome aberration assay, and equivocal in the *in vivo* mouse bone marrow micronucleus assay.

Studies in rabbits, mice, and rats using intramuscular doses up to 1, 33, and 2 mg/kg, respectively, resulted in dose-related increases in fetal resorptions in rabbits and mice.

References

Schacke H, Schottelius A, Docke W-D, *et al.* 2004. Dissociation of transactivation from transrepression by a selective glucocorticoid receptor agonist leads to separation of therapeutic effects from side effects. PNAS 101:227-232.

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/s/

JILL C MERRILL
12/07/2015

BARBARA A HILL
12/07/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208079 **Applicant:** Promius Pharma, LLC **Stamp Date:** 4/06/2015

Drug Name: Betamethasone Dipropionate Spray, 0.05% **NDA Type:** 505(b)(2)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		Formatted to allow substantive review.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		Indexed and paginated to allow substantive review.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	Y		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Y		
6	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 applicant submitted a rationale to justify the alternative route?	Y		
7	Has the applicant 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?	Y		Under Section 2.4.1 the sponsor states: These studies were conducted in compliance with Good Laboratory Practices (GLP) regulations.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	Y		Section 8 is written using the new PLLR format. Section 13 does not include information regarding the 13-week rat study on the basis for which the carcinogenicity waiver was granted.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Y		
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

None.

It is recommended that the following comment be relayed to the sponsor in the 74-day letter.

The dermal carcinogenicity study waiver for your drug product was granted under IND 104853 (4-22-2015). You should resubmit labeling for your drug product that incorporates the results from the 13 week dermal rat toxicity study (study # 13-2355) that the waiver was based on into Section 13.1.

Jill Merrill 5-22-2015

Reviewing Pharmacologist Date

Barbara Hill see sign-off date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

JILL C MERRILL
05/27/2015

BARBARA A HILL
05/27/2015