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APPLICATION NUMBER:

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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/BLA REVIEW AND EVALUATION

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Product: Desoximetasone Spray, 0.25%
Indication: (b) (4) plaque psoriasis in patients
18 years of age or older
Applicant: Taro Pharmaceuticals USA Inc.
Review Division: Dermatology and Dental Products
Reviewer: Renqin Duan, PhD
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TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	4
1.1	INTRODUCTION	4
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	4
1.3	RECOMMENDATIONS	5
2	DRUG INFORMATION	7
2.1	DRUG	7
2.2	RELEVANT INDs, NDAs, BLAs AND DMFs	8
2.3	DRUG FORMULATION	8
2.4	COMMENTS ON NOVEL EXCIPIENTS	9
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	9
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	10
2.7	REGULATORY BACKGROUND	10
3	STUDIES SUBMITTED.....	10
3.1	STUDIES REVIEWED.....	10
3.2	STUDIES NOT REVIEWED	11
3.3	PREVIOUS REVIEWS REFERENCED.....	11
4	PHARMACOLOGY	11
4.1	PRIMARY PHARMACOLOGY	11
4.2	SECONDARY PHARMACOLOGY	11
4.3	SAFETY PHARMACOLOGY	11
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	12
5.1	PK/ADME.....	12
5.2	TOXICOKINETICS	13
6	GENERAL TOXICOLOGY.....	13
6.1	SINGLE-DOSE TOXICITY	14
6.2	REPEAT-DOSE TOXICITY	14
7	GENETIC TOXICOLOGY	23
7.1	<i>IN VITRO</i> REVERSE MUTATION ASSAY IN BACTERIAL CELLS (AMES).....	23
7.2	<i>IN VITRO</i> ASSAYS IN MAMMALIAN CELLS	25
7.3	<i>IN VIVO</i> CLASTOGENICITY ASSAY IN RODENT (MICRONUCLEUS ASSAY).....	29
7.4	OTHER GENETIC TOXICITY STUDIES.....	31
8	CARCINOGENICITY	31
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	31
9.1	FERTILITY AND EARLY EMBRYONIC DEVELOPMENT	32
10	SPECIAL TOXICOLOGY STUDIES.....	38

11 INTEGRATED SUMMARY AND SAFETY EVALUATION..... 38

12 APPENDIX/ATTACHMENTS..... 39

1 Executive Summary

1.1 Introduction

The sponsor submitted a 505(b)(1) NDA application for desoximetasone spray, 0.25%, a new dosage form, which is indicated for the (b) (4) plaque psoriasis in patients 18 years of age or older.

1.2 Brief Discussion of Nonclinical Findings

The sponsor has ownership of all the nonclinical toxicology data contained in NDAs 17856, 18763, and 18568 for the various desoximetasone topical formulations to support this NDA. The sponsor submitted a 28 day repeat dose dermal toxicity bridging study in minipigs conducted with desoximetasone spray and cream, 0.25%, an ICH standard battery of genetic toxicology studies and a subcutaneous fertility study in rats.

Following 28 days of dermal administration of desoximetasone spray, 0.25% and desoximetasone cream, 0.25% to Göttingen minipigs at the same daily dose level of 0.33 mg/kg, no significant differences in toxicological profile were revealed. The signs of toxicity observed were decreases in adrenal weights and reversible atrophic changes in the adrenal gland and/or thymus, which were present in all treated groups. These observations are consistent with results from previous repeat dose toxicity studies and are known pharmacological effects of desoximetasone, resulting from the HPA axis suppression. Signs of application site irritation were no more frequent in desoximetasone treated groups than in vehicle control group. Toxicokinetic analysis demonstrated that dermal administration of desoximetasone spray, 0.25% resulted in greater systemic exposure to active drug than desoximetasone cream, 0.25% (C_{max} and AUC_{0-24} values were approximately 2-fold greater for the spray formulation). There are no clear gender differences in TK parameters within a dose or formulation.

Desoximetasone revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster ovary cell chromosome aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Long-term animal studies have not been performed to evaluate the carcinogenic potential of desoximetasone. The sponsor committed to conduct a 2 year dermal carcinogenicity study in rats as a post-marketing requirement.

No evidence of impairment of fertility was observed in male and female Sprague-Dawley rats by subcutaneously doses up to 0.1 mg/kg/day desoximetasone.

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

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration in doses 3 to 30 times the human dose of Topicort (desoximetasone cream USP) 0.25% and 15 to 150 times the human dose of Topicort (desoximetasone cream USP) 0.05%, or Topicort (desoximetasone gel USP) 0.05%.

Desoximetasone spray, 0.25% does not contain any novel excipients. None of the impurities in the drug substance are above the ICH qualification threshold. Impurities (b) (4) in the proposed drug product are above the ICH qualification threshold. However, there are no concerns from a pharmacology/toxicology perspective based on the nonclinical data and justification the sponsor provided.

1.3 Recommendations

1.3.1 Approvability

Desoximetasone spray, 0.25% is approvable from a pharmacological/toxicological perspective provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the desoximetasone spray, 0.25% label.

1.3.2 Additional Non Clinical Recommendations

Post-Marketing Requirements

The sponsor will perform a 2 year dermal carcinogenicity study in rats as a post-marketing requirement. The sponsor intends to conduct 28 and 90 day dose range finding studies to determine the appropriate maximum tolerated dose to be used in this 2 year dermal carcinogenicity study. The carcinogenicity study protocols and supporting data will be submitted to the Division for review by the Executive Carcinogenicity Assessment Committee. The Sponsor submitted a timeline in response to the 74 day letter sent on September 28, 2012. The proposed timeline is provided in the following table.

Submission of Final Study Protocol (after completion of dose range-finding studies and CAC review)	30 April 2015
Completion of 2-year rat study (in-life)	31 May 2017
Submission of Final Study Report	31 May 2018

Reviewer's comment: The proposed timeline appears acceptable from a pharmacology/toxicology perspective.

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the desoximetasone spray, 0.25% label reproduced below. The nonclinical portions of the label (i.e., sections 8.1, 12.1 and 13.1) are the same as or derived from desoximetasone cream USP, 0.25% label revised in April 2004.

INDICATIONS AND USAGE

Topicort ^{(b) (4)} Topical Spray; ^{(b) (4)} is a ^{(b) (4)} ~~topical~~ corticosteroid formulation indicated for the relief of ^{(b) (4)} plaque psoriasis in patients 18 years of age or older.

Reviewer comment: The pharmacologic class designation of ^{(b) (4)} in the Highlights section of the Topicort Topical Spray, 0.25% label is not consistent with the established pharmacologic class designation. Reviewer recommended changes are provided for this section of the Topicort Topical Spray, 0.25% label.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C:

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

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

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration at doses 3 to 30 times the human dose of Topicort Topical Spray based on a body surface area comparison.

^{(b) (4)}

Reviewer comment: Reviewer recommended changes are provided for this section.

12 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 in psoriasis is unknown.

(b) (4)

Reviewer comment: Reviewer recommended changes are provided for this section.

13 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) -Topicort Topical Spray or desoximetasone.

Desoximetasone revealed no evidence of mutagenic or clastogenic potential based on the results of two (b) (4) in vitro genotoxicity tests (b) (4) (Ames assay and Chinese hamster ovary cell chromosome aberration assay) (b) (4) and (b) (4) one in vivo genotoxicity test (mouse bone marrow micronucleus (b) (4) assay).

No evidence of impairment of male or female fertility was observed at subcutaneous desoximetasone doses up to 0.1 mg/kg/day (0.6 mg/m²/day) in (b) (4) Sprague-Dawley rats. (b) (4)

Reviewer comment: The proposed text in the first paragraph under "Section 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility" is derived from the first paragraph under the "Carcinogenesis, Mutagenesis, and Impairment of Fertility" section of the previously approved label. The proposed text in the second and third paragraphs under "Section 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility" is based on the findings of new toxicology studies the sponsor submitted under this NDA. Reviewer recommended changes are provided for this section.

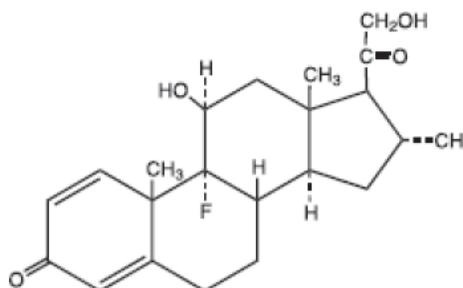
2 Drug Information

2.1 Drug

CAS Registry Number

382-67-2

Generic Name	Topicort (desoximetasone) Topical Spray, 0.25%
Code Name	HOE 304
Chemical Name	Pregna-1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11 β , 16 α)-.
Molecular Formula/Molecular Weight	C ₂₂ H ₂₉ FO ₄ /376.47
Structure	



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

- 1) IND 101789 (TOPICORT {desoximetasone} spray, 0.25%)
- 2) NDA 17-856 (Topicort[®] {desoximetasone} emollient cream, 0.25%)
- 3) NDA 18-309 (Topicort[®] {desoximetasone} LP emollient cream, 0.05%)
- 4) NDA 18-586 (Topicort[®] {desoximetasone} gel, 0.05%)
- 5) NDA 18-763 (Topicort[®] {desoximetasone} ointment, 0.25%)

2.3 Drug Formulation

Each gram (b) (4) of TOPICORT (desoximetasone) spray, 0.25% contains 2.5 mg of desoximetasone in a clear liquid with the inactive ingredients as listed in the following table.

Components and Composition of Drug Product

Strength (Label claim):	0.25% w/w	
Component and Quality Standard	Quantity per unit (mg/g)	% (w/w)
Desoximetasone, USP	2.5	(b) (4)
Glyceryl Oleate, Taro	(b) (4)	
Isopropyl Alcohol, USP		
Isopropyl Myristate, NF		
L-Menthol, USP		
Mineral Oil, USP		
Total Weight		100%

2.4 Comments on Novel Excipients

Desoximetasone spray, 0.25% does not contain any novel excipients.

2.5 Comments on Impurities/Degradants of Concern

None of the proposed acceptance limits for the impurities/degradants in the drug substance are above the ICH recommended limit.

The proposed acceptance limits for the impurities/degradants in the drug product are as follows.

Drug Product Release Limits:

The proposed drug product impurity limits are as follows:

Impurity (b) (4) NMT (b) (4)

Impurity (b) (4) NMT (b) (4)

Individual unidentified impurities: NMT (b) (4)

Total impurities: NMT (b) (4)

Drug Product Stability Limits:

The proposed drug product stability impurity limits are as follows:

Impurity 2: NMT (b) (4)

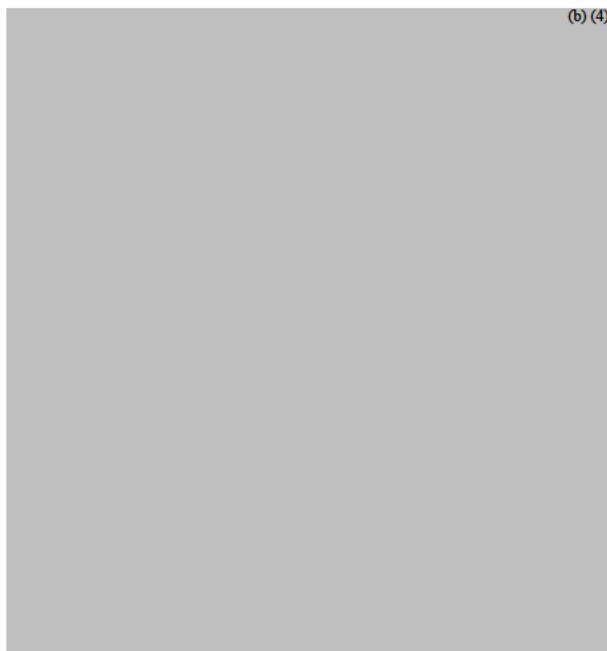
Impurity 3: NMT (b) (4)

Individual unidentified impurities: NMT (b) (4)

Total impurities: NMT (b) (4)

(b) (4)

The proposed acceptance limits for impurities in the drug product for the release testing are not above the ICH recommended limit. However, the proposed drug product stability acceptance limits for impurities (b) (4) and (b) (4) are above the ICH recommended impurity limit. The sponsor stated that that impurity (b) (4) (b) (4) This metabolite is inactive, water soluble and rapidly eliminated from the system. Therefore, this impurity has negligible pharmacological/toxicological activities and does not raise any safety concern.



Impurity 3 (Oxidation impurity)

The CMC reviewer, Dr. Hamid Shafiei expressed his concerns with these specifications for impurities (b) (4) in the drug product in an email communication. This reviewer stated that the justification the sponsor provided for impurities (b) (4) appears reasonable and the proposed acceptance limits for impurities (b) (4) appears acceptable from a pharmacology/toxicology perspective based on the nonclinical data available.

2.6 Proposed Clinical Population and Dosing Regimen

Desoximetasone spray, 0.25% is a topical corticosteroid formulation indicated for the relief of (b) (4) plaque psoriasis in patients 18 years of age or older. Desoximetasone spray, 0.25% is applied as a thin film to the affected skin area twice daily.

2.7 Regulatory Background

The sponsor submitted an Investigational New Drug application (IND 101,789) for desoximetasone spray, 0.25% on February 27, 2008. The Division requested that a number of nonclinical studies be performed in support of an eventual NDA in a facsimile dated May 9 2008. The Division also indicated that carcinogenicity studies would be required post-marketing. There was not an End-of-Phase 2 meeting for this drug product. There was a Pre-NDA meeting on July 20, 2011. The sponsor committed to conduct a 2 year dermal carcinogenicity study in rats as a post-marketing requirement.

3 Studies Submitted

3.1 Studies Reviewed

General Toxicology

1. A 28-Day Dermal Bridging Toxicity Study Followed by a 28-Day Recovery of Desoximetasone Spray 0.25% in the Göttingen Minipig (Study No.: 60428)

Genetic Toxicology

1. Desoximetasone: Bacterial Reverse Mutation Test (Study No.: G6405)
2. Desoximetasone: *In Vitro* Mammalian Chromosome Aberrations in CHO Cells (Study No.: G6406)
3. Desoximetasone: Mammalian Erythrocyte Micronucleus Test by Gavage in Swiss Albino Mice with Plasma Exposure Assessment (Study No.: G6407)

Reproductive and Developmental Toxicology

1. Effect of Subcutaneous Injections of Compound HOE 304 as Compared to dexamethasone on the Fertility, Pregnancy and Postnatal development of Rats (Study No.: Experiment 0575-54)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

The pharmacological effects of desoximetasone, a synthetic corticosteroid that is currently approved and marketed in a number of topical formulations, are well known. Since desoximetasone spray, 0.25%, is the same dose and route of administration as currently approved and marketed formulations, no new primary, secondary or safety pharmacologic effects or concerns are expected.

4.1 Primary Pharmacology

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

4.2 Secondary Pharmacology

Desoximetasone spray, 0.25% is a topical corticosteroid that has been shown to produce hypothalamic-pituitary-adrenal (HPA) axis suppression.

4.3 Safety Pharmacology

No safety pharmacology studies were conducted with desoximetasone spray, 0.25%. Per the sponsor, Electrocardiograms (ECG) were obtained during a 6 month toxicity study in Beagle dogs conducted in support of NDA 17-856. Following subcutaneous

dosing for 6 months (0.2, 0.4, 0.8 mg/kg/day; n=4/sex/group), no effect on heart rate or PQ or QT intervals was detected.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The sponsor conducted two GLP toxicity studies in which the toxicokinetics (TK) of desoximetasone were determined. One study was performed in Göttingen minipigs given repeated topical administration of desoximetasone spray, 0.25% over 28 days (using the same formulation used in clinical trials and proposed for marketing). The other study was performed in Swiss Albino mice dosed orally with a suspension of desoximetasone as part of an in vivo micronucleus assay. Additional information on the systemic disposition of desoximetasone is available from a study performed in support of desoximetasone cream, 0.25% (NDA 17-856). It was performed in Wistar rats that were dosed subcutaneously with radiolabeled desoximetasone.

Absorption

Desoximetasone was absorbed slowly and systemic exposure was low after topical administration of desoximetasone spray, 0.25% to minipigs. After the first application, concentrations appeared to plateau between 2 to 4 hours post-dose. Accumulation with repeated dosing was apparent. Increases in systemic exposure ($AUC_{0-24 \text{ hr}}$) were less than dose proportional. Systemic exposure was greater after topical application of the desoximetasone spray formulation (0.33 mg/kg/day) compared to the desoximetasone cream formulation (0.33 mg/kg/day) in minipigs.

Mean Plasma Toxicokinetic Parameters in Minipigs Following Administration of Desoximetasone Spray, 0.25% and Cream, 0.25% (N=4/sex/group)

Desoximetasone Dose (mg/kg/day)	Gender	Day 1			Day 28		
		C_{\max} (ng/mL)	T_{\max} (hr)*	AUC_{0-24} (ng·hr/mL)	C_{\max} (ng/mL)	T_{\max} (hr)*	AUC_{0-24} (ng·hr/mL)
0.33 (Low Dose) Spray	F	0.406	6-12	4.473	4.514	0-8	63.794
	M	0.314	8-12	5.310	4.705	2-8	59.425
1.00 (High Dose) Spray	F	0.532	8-12	8.518	6.810	1-8	101.363
	M	0.649	6-12	11.035	6.780	2-8	104.624
0.33 (Low Dose) Cream	F	0.176	2-24	2.142	2.033	2-8	32.236
	M	0.113	12-24	1.552	2.232	2-6	36.242

Source: ITR Study No 60428, Appendix II Bioanalytical report and toxicokinetic analysis, Tables 6 – 8

*Range; it is to be noted that animals received a second dose 5 hours after the first dose.

Distribution

Upon absorption, topical corticosteroids are processed through pharmacokinetic pathways similar to systemically administered corticosteroids.

In a study performed in support of the original approval of Topicort (desoximetasone) cream (NDA 17-856), ³H-desoximetasone (dissolved in sesame oil) was administered subcutaneously to male Wistar rats (n=5) in a dose of 0.54 mg/kg. Animals were sacrificed 7 days later and the concentrations of radioactivity in the tissues were found to be very low. With the exception of the skin at the injection site, concentrations in examined tissues were below or near the limit of detection (<5 ng-equiv/g).

Metabolism

Desoximetasone is primarily metabolized in the liver.

Elimination / Excretion

Desoximetasone is excreted in the urine and feces.

Once systemically absorbed, elimination of desoximetasone from the plasma is rapid in rats dosed subcutaneously (plasma T_{1/2} of 2.3 hours). The dose is eliminated in the urine and feces in approximately equal amounts within 24 hours. Levels of radioactivity fell below the limit of detection (0.3%, based on administered radioactivity) within 2 days in urine and 3 days in feces

In minipigs, the apparent plasma T_{1/2} at steady state appears longer (approximately 12 hours). However, this is likely confounded by continued absorption from the dermal application site.

5.2 Toxicokinetics

(See section 6.2 for the details)

6 General Toxicology

The toxicity profile of desoximetasone is similar to other corticosteroids. The following local adverse reactions have been noted clinically with the use of topical corticosteroids: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae and malaria. Systemic absorption of topical corticosteroids has produced hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients.

Desoximetasone, first approved in the United States in 1977 as Topicort[®], is a synthetic corticosteroid marketed in a number of formulations: gel (0.05%), cream (0.05% and 0.25%), and ointment (0.05% and 0.25%). The sponsor acquired the Topicort[®] brand in 2003 and has ownership of all the nonclinical toxicology data contained in NDAs 17856, 18763, and 18568 for these desoximetasone topical formulations to support this NDA.

A 3 week repeat dose dermal toxicity study was performed with desoximetasone cream, 0.25% in rats. Three repeat dose dermal toxicity studies were performed with desoximetasone ointment, 0.25%, two 20 day studies in rabbits and one 6 month study

in dogs. In addition, studies of local toxicity were performed in rabbits and dogs. The expected local and systemic glucocorticoid effects were observed in these studies. Local effects included thinning of the epidermis, atrophic changes in the hair follicle and reddening of the skin at the application site (due to vehicle) as well as epilation and erosion at the application site and erythema and hyalinization of the hair follicle. Similar systemic effects were observed across species and included decreased body weights, decreased adrenal and thymus weights, thymic atrophy, fatty liver and decreased leukocytes. In White New Zealand rabbits, effects on the myocardium were also noted at all dose groups (≥ 0.0125 mg/kg) (inflammation, degeneration, and necrosis in one study each).

Repeat dose studies have also been performed with the oral and subcutaneous routes in rats and dogs. Following repeated oral dosing of desoximetasone to Wistar rats for 2 weeks to three months, decreased body weights and adrenal and thymus weights were seen at doses ≥ 0.05 mg/kg/day. Three months of oral dosing (≥ 0.1 mg/kg/day) resulted in decreases in blood glucose and leukocytes and increases in hematocrit and hemoglobin. A dose of 0.4 mg/kg/day was lethal to Wistar rats; all animals at this dose level died of pulmonary infections within 2 months of study initiation. Subcutaneous administration of desoximetasone to Sprague-Dawley rats for six months (0.05 – 0.5 mg/kg/day) resulted in findings similar to oral dosing. Six months of subcutaneous dosing (0.2, 0.4, 0.8 mg/kg/day) in the Beagle dog (n=4/sex/group), resulted in findings similar to those described for rats as well as sedation, decreased cortisol levels and ECG abnormalities.

The sponsor conducted a 28 day repeat dose dermal bridging toxicity study in Göttingen Minipigs with desoximetasone spray and cream, 0.25% (see Section 6.2 for the details). There was no apparent difference in the toxicity profile between the proposed desoximetasone spray, 0.25% and the approved desoximetasone cream, 0.25% based on the results of the 28 day repeat dose dermal toxicity bridging study in minipigs.

6.1 Single-Dose Toxicity

No single-dose toxicity studies were conducted with desoximetasone spray, 0.25%. The oral desoximetasone LD₅₀ reported in mice, rats, and rabbits were 1519 mg/kg, 230 to 1469 mg/kg, and 2546 mg/kg, respectively.

6.2 Repeat-Dose Toxicity

Study title: A 28-Day Dermal Bridging Toxicity Study Followed by a 28-Day Recovery of Desoximetasone Spray 0.25% in the Göttingen Minipig

Study no.:	60428
Study report location:	Electronic submission, SDN 1
Conducting laboratory and location:	 (b) (4)

Date of study initiation: 02-03-2009
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Desoximetasone Spray 0.25%, lot# L163-57868
Desoximetasone Cream 0.25%, lot#D8008

Key Study Findings

No significant differences in toxicological profile were noted following 28 days of dermal administration of desoximetasone spray, 0.25% or desoximetasone cream, 0.25% to Göttingen minipigs at the same daily dose level of 0.33 mg/kg. The signs of toxicity observed were decreases in adrenal weights and reversible atrophic changes in the adrenal gland and/or thymus, which were present in all treated groups. These observations are consistent with results from previous repeat dose toxicity studies and are known pharmacological effects of desoximetasone, resulting from the HPA axis suppression. Although no thymic atrophy was noted following cream administration, only one of the animals treated at the same dose level with the spray showed this finding. Administration of the spray formulation at a higher dose of 1.00 mg/kg/day did reveal a higher incidence of changes in parameters measured in this study compared to lower dose treated groups.

Signs of application site irritation were no more frequent in desoximetasone treated groups than in vehicle control group. The dermal changes observed were considered procedure related and not attributable to test article.

Toxicokinetic analysis demonstrated that dermal administration of desoximetasone spray, 0.25% resulted in greater systemic exposure to active drug than desoximetasone cream, 0.25% (C_{max} and AUC_{0-24} values were approximately 2-fold greater for the spray formulation). However, the extent of absorption was minimal and there was no significant difference in the toxicity profile between the desoximetasone spray and cream formulations. There were no clear gender differences in TK parameters noted in this study.

Methods

Doses: See the table below
Frequency of dosing: Twice daily
Route of administration: Topical
Dose volume: See the table below
Formulation/Vehicle: Clinical spray formulation used/ Desoximetasone spray vehicle
Species/Strain: Göttingen Minipig
Number/Sex/Group: 3
Age: 3 to 4 months old
Weight: Males: 8.0 to 9.3 kg; Females: 8.0 to 9.5 kg
Satellite groups: 1/Sex/Group for recovery

Unique study design: N/A
 Deviation from study protocol: There were no protocol deviations that were considered to have compromised the validity or integrity of the study.

Group Numbers	Group Designation	Dose Formulation (mg/kg/day)*	Dose Desoximetasone (mg/kg/day)	Desoximetasone Concentration (mg/g)	Main		Recovery	
					Male	Female	Male	Female
1	Control – Desoximetasone Spray Vehicle	133	0	0	3	3	1	1
2	Formulation I– Desoximetasone Spray 0.25% (Low Dose)	133	0.33	2.5	3	3	1	1
3	Formulation I– Desoximetasone Spray 0.25% (High Dose)	400	1.00	2.5	3	3	1	1
4	Formulation II– Desoximetasone Cream 0.25%	133	0.33	2.5	3	3	1	1

* = Half of the total dose was administered at each dose (5 hours apart)

Observations and Results

Mortality

Mortality checks were performed at least once a day during all phases of the study.

There was no mortality in this study.

Clinical Signs

Cage-side clinical signs were recorded once a day during all phases of the study except on detailed clinical examination days. A detailed clinical examination of each minipig was performed once pretreatment, weekly during the treatment and recovery periods and prior to necropsy.

There were no adverse clinical signs that could be attributed to the topical administration of desoximetasone spray and cream 0.25%. Various findings that were observed among the treated animals were not considered to be toxicologically significant since they were either seen during the pre-treatment period and/or in control animals, or they were findings typically seen in comparable populations of normal minipigs.

Dermal Observation

Dermal changes were assessed daily (excluding Day 1) for all animals prior to dosing (first dose) and during the recovery period. Any abnormalities were recorded.

There were isolated signs of irritation. Observations included reddening of the skin (described as red spots), desquamation and scab/crust formation, erythema and edema of slight to moderate severity. However, these were observed during the treatment and recovery periods in both control and treated individuals and in both sexes but with a higher incidence in the females. The locations of these spots varied as they were found at the dermal test site in some animals and at the dermal test site and/or outside the marked treated area in other animals. The pattern of change noted during the study suggests that they are procedure related and not indicative of test article related irritation.

For one animal in the Control Group, from Day 16 moderate to severe erythema, slight edema, some desquamation and scab/crust formation were observed on the whole dosing site. These changes were considered to be related to study procedures and not indicative of irritation for the vehicle as no other animal showed a similar reaction.

Body Weights

Body weights were recorded for all animals once prior to group assignment, and approximately one week prior to initiation of treatment. Body weights were recorded for all animals up to 1 day prior to dosing and at least weekly thereafter during the treatment and recovery periods, as well as terminally prior to necropsy (fasted).

There was no significant treatment related adverse effect on body weights and body weight gains for all the animals.

Feed Consumption

Food consumption was measured daily during the week prior to treatment and daily during the treatment and recovery periods.

The topical administration of Desoximetasone Spray 0.25% and Cream 0.25% had no effect on food consumption.

Ophthalmoscopy

N/A

ECG

N/A

Hematology

Hematology parameters were measured on blood samples (nominal 1 mL) collected into EDTA anticoagulant at termination on all Main and Recovery animals.

Changes were observed in some hematological parameters. However, none of them were considered toxicologically significant.

Coagulation

Coagulation parameters were measured on blood samples (nominal 1.3 mL) collected into citrate anticoagulant at termination on all Main and Recovery animals.

No test article related adverse effects on any coagulation parameters were observed during the study.

Clinical Chemistry

Clinical chemistry parameters were measured on blood samples (nominal 1.1 mL) collected into tubes containing clotting activator at termination on all Main and Recovery animals.

Significant reduction in alkaline phosphatase (ALP) was predominantly observed in male animals treated with the spray formulation at 0.33 mg/kg/day (53% decrease comparing to vehicle control: 97 vs 207) and 1.00 mg/kg/day (74% decrease comparing to vehicle control: 53 vs 207). 52% decrease in ALP was also observed in female animals treated with the spray formulation at 1.00 mg/kg/day (60 vs 126). However, evaluation of samples collected at the end of the recovery period (Day 57) revealed no significant difference in ALP levels among the treatments.

No other significant treatment related effects on clinical chemistry parameters were noted in this study.

Urinalysis

Laboratory urinalysis was performed at termination on all Main and Recovery animals. Urine samples were recovered, when available, by cystocentesis during the necropsy procedure.

There were no significant treatment related changes noted in any of the urinalysis parameters following the topical administration of Desoximetasone Spray and cream 0.25%.

Gross Pathology

All animals were euthanized upon completion of the treatment/recovery periods and following an overnight period without food. All surviving animals were pre-anesthetized with a cocktail of ketamine, acepromazine and atropine and then euthanized by an intravenous overdose of sodium pentobarbital followed by exsanguination by severance of major blood vessels. Gross pathology consisted of an external examination, including identification of all clinically recorded lesions, as well as a detailed internal examination. A staff pathologist was available for consultation during all necropsies.

There were no treatment related effects on macroscopic parameters noted in this study.

Organ Weights

All animals were euthanized at termination and organs identified in the table below were dissected, trimmed free of fat and weighed. Absolute and relative organ weights (relative to terminal body weight) were calculated.

In comparison with the vehicle control values, evaluation of organ weights on Day 29 revealed a significant decrease in absolute and relative adrenal weights in all treated males and desoximetasone spray treated females (see the table below). An increase in the relative testis weight was also observed in desoximetasone spray treated males (see the table below).

Effects on Organ Weights on Day 29					
Organ weights	Sex	Control	Group 2	Group 3	Group 4
Adrenal (g)	Male	1.031	0.754	0.695	0.7
%decrease			23	33	32
	Female	1.041	0.771	0.723	1.011
			26	31	
Adrenal to BW	Male	0.01	0.0076	0.0076	0.0074
%decrease			24	24	26
	Female	0.0098	0.0074	0.0078	0.0098
			24	20	
Testes to BW		0.3448	0.4391	0.4356	0.401
%increase			27	26	16

No other treatment related effects on organ weights were observed in this study.

At the end of the recovery period (Day 57) the decrease in adrenal weights was only apparent in group 3 males and group 2 females, which suggested there was partial recovery. There was still a significant increase in the relative and absolute testis weights for Group 3 and 4 male animals (see the table below).

Effects on Organ Weights on Day 57

Organ weights	Sex	Control	Group 2	Group 3	Group 4
Adrenal (g)	Male	1.087	1.096	0.84	0.994
%decrease			n/a	23	9
	Female	1.204	0.945	1.104	1.287
			21	8	n/a
Adrenal to BW	Male	0.0091	0.0094	0.0075	0.0092
%decrease			n/a	18	n/a
	Female	0.0104	0.0077	0.009	0.0111
			26	13	n/a
Testes (g)		33.16	30.636	49.851	51.727
%increase			n/a	50	56
Testes to BW		0.2787	0.2641	0.4451	0.479
%increase			n/a	60	72

Histopathology

Adequate Battery: Yes

On completion of the gross examination and selected organ weighing, the tissues and organs noted in the table below were retained. Neutral buffered 10% formalin was used for fixation and preservation unless otherwise indicated. Histopathological examination was performed on all animals (Main and Recovery).

ORGANS/TISSUES	Retain (*)	Weigh (√)	Examine (€)	ORGANS/TISSUES	Retain (*)	Weigh (√)	Examine (€)
Adrenals	-	√	€	Duodenum	-		€
Animal identification	-			Jejunum	-		€
Aorta (thoracic)	-		€	Ileum	-		€
Blood				SC, cervical	-		€
Bone marrow smears (3)	-			Spleen	-	√	€
Brain	-	√	€	Sternum & marrow	-		€
Cecum	-		€	Stomach	-		€
Colon	-		€	Testes	*d	√	€
Epididymides	*d		€	Thymus+ parathyroids	-	√	€
Esophagus	-		€	Thyroid gland	-	√	€
Eyes	*a		€	Tongue	-		€
Femur & marrow	-		€	Trachea	*c		€
Gallbladder	-		€	Urinary bladder	-		€
Heart	-	√	€	Uterus	-	√	€
Kidneys	-	√	€	Vagina	-		€
Liver (2 lobes)	-	√	€	Bulbourethral glands	-		€
Lungs (with bronchi) (2 lobes)	*bc	√	€	Vesicular glands	-		€
LN, mandibular	-		€				
LN, mesenteric	-		€	Abnormal findings	-		€
Mammary gland (inguinal)	-		€	Additional Tissues presented below			
Optic nerves	*a		€	Treated and non-treated dermal sites from each animal (an area of approximately 2cm x 2cm from the central area of the dosing area)	-		€
Ovaries	-	√	€				
Pancreas	-		€				
Pituitary	-	√	€				
Prostate	-	√	€				
Rectum	-		€				
SG, mandibular	-		€				
Sciatic nerve	-		€				
Skeletal muscle	-		€				
Skin & subcutis (inguinal)	-		€				
a	Davidson's fluid						
b	Lungs were infused with 10% neutral buffered formalin						
c	Lungs were weighed with trachea and recorded in Provantis as lungs (with bronchi) in organ weight record						
d	Bouin's fluid						
LN	Lymph node						
SG	Salivary gland						
SC	Spinal cord						
€	Examine microscopically						
Notes:							
Paired organs weighed together							
Parathyroids and mammary gland were examined histologically where present.							

Peer Review: N/A

Histological Findings

Microscopic findings for Groups 2 and 3 (desoximetasone spray 0.25%, 0.33 and 1.00 mg/kg/day, respectively) revealed treatment-related minimal to mild adrenal cortical atrophy (zona fasciculata) observed in 1 (male) of 6 Group 2 animals (desoximetasone spray 0.25%, 0.33 mg/kg/day) and 5 (three males and two females) of 6 Group 3 animals (desoximetasone spray 0.25%, 1.00 mg/kg/day). Generally, this change correlated with decreased adrenal organ weight. Additionally, minimal to mild thymic atrophy was noted in 1/5 Group 2 (one male) and 2/3 Group 3 (one male and one female) animals. Although the number of animals per group was small, the occurrence of this finding in one Group 2 and two Group 3 animals and absence of this finding in control animals suggests a test article-related effect. For Group 4 (desoximetasone

cream 0.25%, 0.33 mg/kg/day) treatment-related minimal adrenal cortical atrophy (zona fasciculata) was observed in 2/6 (male only) animals.

Special Evaluation

N/A

Toxicokinetics

A series of 8 blood samples (approximately 6 mL each) was removed from each minipig on Days 1 and 28 of the treatment period. Each minipig was bled by venipuncture (cranial vena cava) and the samples were collected into tubes containing the anticoagulant, K₂EDTA. The tubes were placed on wet ice pending processing. Samples were collected at pre-treatment, 1, 2, 4, 6, 8, 12 and 24 hours after the first treatment (i.e. after the first topical application).

Following collection, the samples were centrifuged (approximately 4°C) and the resulting plasma was recovered and stored frozen, within one hour of collection, at approximately -80°C in labeled polypropylene tubes (3.5 mL).

The peak plasma concentrations of desoximetasone were observed between 0-24 hours depending on the dose and whether the product was applied as a spray or cream. In the case of low dose spray, the maximum concentration occurred between 6-12 hours after the first exposure while after 28 days of exposure the time to maximum concentration occurred between 0-8 hours. In the case of high dose spray the time to maximum concentration occurred between 6-12 hours after the first exposure and between 1-8 hours after 28 days of exposure. In the case of cream the time to maximum concentration occurred between 0-24 hours after first exposure and 2-8 hours after 28 days of exposure.

No clear differences were observed between male and female animals within a dose or formulation but there was a difference between the cream and spray formulations. In this regard the cream appeared to reach maximal concentration later than the two spray formulations after the first exposure but then reached maximal concentration at a similar time to the two spray formulations after 28 days of exposure.

At day 28 all three groups of animals (i.e. animals treated with the desoximetasone spray at 0.33 mg/kg/day and 1.00 mg/kg/day and desoximetasone cream at 0.33 mg/kg/day) demonstrated clearly distinct plasma concentration time profiles that not only revealed differences in C_{max} and AUC_{0tolast} but also showed secondary peaks corresponding to the second daily dose administered five hours after the initial dose on that day. The levels of desoximetasone declined such that at 24 hours they reached a value close to that observed for the zero hour sample on that day. The plasma concentration time profiles for both male and female animals within a formulation group also did not demonstrate any clear difference between males and females. There was a 10-12 fold increase in C_{max} and AUC_{0tolast} from Day 1 to Day 28 when the spray formulations were compared, while the cream formulation demonstrated a 17 and 21 fold increases in C_{max} and AUC_{0tolast} respectively across this same period of time.

C _{MAX}		Day 1	Day 28
Cream	Mean	122.65	2132.41
	Median	110	2033
	SD	87.94	692.68
Low Dose	Mean	360.08	4609.34
	Median	203	4876
	SD	225.73	2259.24
High Dose	Mean	590.24	6795.07
	Median	530	6197
	SD	272.40	1577.36

AUC 0-last		Day 1	Day 28
Cream	Mean	1579.29	34239.18
	Median	1452	35096
	SD	1034.22	11076.03
Low Dose	Mean	4891.53	61609.38
	Median	4695	69429
	SD	2161.15	24477.57
High Dose	Mean	9776.38	102993.50
	Median	8426	97823
	SD	4757.08	32015.51

Dosing Solution Analysis

The dosing formulations were provided by the sponsor and used as supplied. Test article concentrations in each formulation were verified by the Sponsor and are indicated in the Certificates of Analysis.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Desoximetasone: Bacterial Reverse Mutation Test

Study no.: G6405
 Study report location: Electronic submission, SDN 1
 Conducting laboratory and location: Mutagenicity

(b) (4)

(b) (4)

Date of study initiation: 02-23-2009
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Desoximetasone USP, lot# RM080483, purity 99.8%

Key Study Findings

Desoximetasone was negative in the Ames assay under the conditions of the study.

Methods

Strains: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA.

Concentrations in definitive study: 0 (DMSO), 100, 266, 707, 1880, and 5000 µg/plate

Basis of concentration selection: The highest concentration tested in the assay, 5000 µg/plate, is the high dose recommended for this assay by the ICH S2(R1) guidance

Negative control: Dimethyl sulphoxide (DMSO) 100µl

Positive control: 1) TA 98 strain – 2-Nitrofluorene (-S9, 2 µg/plate) and 2-Aminoanthracene (+S9, 4 µg/plate)

2) TA 100 strain – Sodium Azide (-S9, 1 µg/plate) and 2-Aminoanthracene (+S9, 4 µg/plate)

3) TA 1535 strain – Sodium Azide (-S9, 1 µg/plate) and 2-Aminoanthracene (+S9, 4 µg/plate)

4) TA 1537 strain – 9-aminoacridine (-S9, 50 µg/plate) and 2-Aminoanthracene (+S9, 4 µg/plate)

5) WP2uvrA strain – 4-nitroquinoline-N-oxide (-S9, 4 µg/plate) and 2-Aminoanthracene (+S9, 30 µg/plate)

Formulation/Vehicle: DMSO
Incubation & sampling time: After all treatments had been performed, the plates were incubated for approximately 67 hours at $37 \pm 1^\circ\text{C}$. Plates were counted for colony formation after completion of the incubation period.

Study Validity

Solvent control mean reversion frequencies fell within established ranges. Appropriate positive controls were used for each bacterial strain. Positive control results were appropriate showing a mean reversion frequency that was more than three times the mean reversion frequency of the solvent control plates. Dose range selected for the definitive study was appropriate according to ICH guidelines. All strains plus or minus S9 activation system were tested in triplicates.

Results

Based upon the results of the dose range-finding assay, desoximetasone was evaluated in the first mutagenicity assay, in all five tester strains, at doses of 50, 158, 500, 1581, and 5000 $\mu\text{g}/\text{plate}$ in the presence and absence of S9 mix using direct plate incorporation procedure. All doses of the test article, as well as the concurrent positive and vehicle controls were evaluated in triplicate plates. No positive increases in the mean number of revertants/ plate were observed for desoximetasone treated plates compared to vehicle control with any of the tester strains in the presence or absence of S9 mix.

Desoximetasone was re-evaluated in the confirmatory (second) mutagenicity assay under identical conditions using pre-incubation procedure. No positive increases in the mean number of revertants/plate were observed for desoximetasone treated plates compared to vehicle control with any of the tester strains in the presence or absence of S9 mix.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Desoximetasone: *In Vitro* Mammalian Chromosome Aberrations in CHO Cells

Study no.:	G6406
Study report location:	Electronic submission, SDN 1
Conducting laboratory and location:	Mutagenicity  (b) (4)
Date of study initiation:	02-23-2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Desoximetasone USP, lot# RM080483, purity 99.8%

Key Study Findings

Desoximetasone was not clastogenic in CHO cells under the conditions of the study.

Methods

Cell line:	Chinese hamster ovary (CHO) cell line
Concentrations in definitive study:	0 (DMSO), 50, 100, 130, 160, and 180 µg/mL for 3 hours with and without metabolic activation and 0 (DMSO), 20, 35, 50, 65, and 80 µg/mL for 21 hours without metabolic activation.
Basis of concentration selection:	Toxicity. Evidence of significant growth inhibition was observed at and above 150 µg/mL with 3 and 21-hour exposure. Dead and disfigured cells were observed at and above 300 µg/mL.
Negative control:	DMSO 300 µl
Positive control:	Ethylmethane sulphonate (EMS), - S9, 600 µg/mL Cyclophosphamide monohydrate (CPA), + S9, 55 µg/mL.
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Chromosome aberration was analyzed with three experiments: 3-hour exposure both with and without S9 activation (experiments 1 and 2) and 21-hour continuous exposure without S9 (experiment 3). Cultures exposed for 3 hours with and without S9 were drained, washed and given fresh medium and harvested about 21 hours after the beginning of test article treatment. Colcemid at 10 µg/mL was added to all the cultures 2 hours before harvesting.

Study Validity

The incidence of aberrations in the vehicle control cultures was in the historical control range. The positive controls induced significant increase in percent of aberrant cells over the corresponding negative control values. There was a minimum of three analyzable concentration levels obtained for each experiment. Thus, data met the criteria for acceptance.

Results

Experiment 1: Presence of metabolic activation

At the highest concentration tested and evaluated (180 µg/mL), the reduction in the cell growth was 52% compared to the vehicle control. The incidence of aberrant metaphases both including and excluding gaps was comparable to the vehicle control in all three tested concentrations.

Treatment (µg/mL)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
DMSO (300 µL)	200	0	4 (2.0)	0	1 (0.5)	0	0	0	5 (2.5)	1 (0.5)	-
50	200	0	5 (2.5)	1 (0.5)	1 (0.5)	0	0	0	6 (3.0)	2 (1.0)	7
130	200	0	5 (2.5)	1 (0.5)	2 (1.0)	0	0	0	8 (4.0)	3 (1.5)	21
180	200	0	4 (2.0)	1 (0.5)	3 (1.5)	0	0	0	8 (4.0)	4 (2.0)	52
CPA 55	200	16 (8.0)	49 (24.5)	52 (26.0)	37 (18.5)	23 (11.5)	33 (16.5)	2 (1.0)	+ 141 (70.5)	+ 109 (54.5)	37

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations

Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome

CPA: Cyclophosphamide monohydrate +: Significantly higher than control ($p \leq 0.05$) by Fisher exact test

Experiment 2: Absence of Metabolic Activation

At the highest concentration evaluated (160 µg/mL), the reduction in the cell growth was 51% compared to the vehicle control. The incidence of aberrant metaphases both including and excluding gaps was comparable to the solvent control at 100 and 130 µg/mL test concentrations compared to the vehicle control. However, at 160 µg/mL, there was a small increase in the incidence of aberrant metaphases both including and excluding gaps compared to the vehicle control.

Treatment ($\mu\text{g/mL}$)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
DMSO (300 μL)	200	0	0	0	0	0	0	0	0	0	-
100	200	0	1 (0.5)	0	0	0	0	0	1 (0.5)	0	9
130	200	0	1 (0.5)	0	1 (0.5)	0	0	0	2 (1.0)	1 (0.5)	19
160	200	1 (0.5)	2 (1.0)	1 (0.5)	6 (3.0)	0	0	0	+ 7 (3.5)	+ 7 (3.5)	51
EMS 600	200	28 (14.0)	43 (21.5)	33 (16.5)	58 (29.0)	11 (5.5)	24 (12.0)	2 (1.0)	+ 106 (53.0)	+ 87 (43.5)	38

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations

Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome

EMS: Ethyl methanesulphonate + : Significantly higher than control ($p \leq 0.05$) by Fisher exact test

Reviewer's comments: Total No. (%) of aberrant metaphase (including Gaps) for 160 $\mu\text{g/mL}$ should be 10 (5.0) instead of 7 (3.5) in the table above.

Experiment 3: Absence of Metabolic Activation

At the highest concentration tested and evaluated (80 $\mu\text{g/mL}$), the reduction in the cell growth was 56% compared to the vehicle control. The incidence of aberrant metaphases both including and excluding gaps was comparable to the vehicle control in all three tested concentrations.

Treatment ($\mu\text{g/mL}$)	No. of metaphases scored	No.(%) of metaphases with aberrations							Total No.(%) of aberrant metaphases*		Cell Growth Inhibition (%)
		Gaps		Breaks		Exchanges			Including Gaps	Excluding Gaps	
		Cs	Ct	Cs	Ct	Cs	Ct	RC			
DMSO (300 μL)	200	0	3 (1.5)	0	0	0	0	0	3 (1.5)	0	-
20	200	0	2 (1.0)	0	0	0	0	0	2 (1.0)	0	2
50	200	0	4 (2.0)	2 (1.0)	1 (0.5)	0	0	0	5 (2.5)	2 (1.0)	18
80	200	0	1 (0.5)	0	0	0	0	0	1 (0.5)	0	56
EMS 600	200	23 (11.5)	63 (31.5)	53 (26.5)	89 (44.5)	11 (5.5)	42 (21.0)	2 (1.0)	+ 132 (66.0)	+ 124 (62.0)	43

* : Metaphase plate with one or more than one aberrations considered as one metaphase plate with aberrations

Cs: Chromosome type Ct: Chromatid type RC: Ring chromosome

EMS: Ethyl methanesulphonate + : Significantly higher than control ($p \leq 0.05$) by Fisher exact test

Discussion and Conclusion

In the experiment excluding metabolic activation with 3-hour exposure, there was a small increase in aberrant metaphases in the data set both including and excluding gaps at 160 µg/mL test concentration. However, the effect was only statistically significant when both chromatid and chromosome gaps were included in the analysis. The status of gaps as true aberrations is a matter of debate and they are often ignored or used as evidence of chromosome damage only in the event of equivocal results. Furthermore, since there were no incidences of any aberrant cells in the concurrent vehicle control, it looks like an isolated incidence of increase in the number of only breaks which can be considered as not biologically significant. Chromosomal exchanges are comparatively rare spontaneous events and have important genetic consequences. In border line situations, therefore, greater significance should be attached to the observation of exchanges in treated cells than to a small numerical increase in gaps and breaks.

The results of the three experiments support a conclusion that the effect is biologically insignificant and the test article does not have the potential to cause chromosome damage either including gaps or excluding gaps and either in the presence or absence of metabolic activation.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Desoximetasone: Mammalian Erythrocyte Micronucleus Test by Gavage in Swiss Albino Mice with Plasma Exposure Assessment

Study no:	G6407
Study report location:	Electronic submission, SDN 1
Conducting laboratory and location:	Toxicology
	
Date of study initiation:	03-19-2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Desoximetasone USP, lot# RM080483, purity 99.8%

Key Study Findings

Desoximetasone was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay under the conditions of this assay.

Methods

Doses in definitive study: 0, 300, 600, and 1200 mg/kg/day
Frequency of dosing: Twice at an interval of 24 hours
Route of administration: Gavage
Dose volume: 20 mL/kg
Formulation/Vehicle: 2 % (w/v) sodium salt of carboxymethyl cellulose (low viscosity) in distilled water with Tween 80 (1 mL/L)
Species/Strain: Mouse/Swiss Albino mouse
Number/Sex/Group: 5
Satellite groups: 6/Sex/Group for vehicle control TK group, 18/Sex/Group for low dose, mid dose and high dose TK groups
Basis of dose selection: Toxicity. A Dose Range Finding (DRF) study was conducted in 2 male and 2 female mice at doses of 0 (vehicle control), 300, 750, 1400 and 2000 mg/kg/day. Mice were treated twice at 24 hour interval with a dosage volume of 20 mL/kg and were sacrificed 20-24 hours after the second treatment.

The body weights were slightly reduced in the 1400 and 2000 mg/kg/day groups when compared to the vehicle control group and the treated mice exhibited clinical signs of dullness, lethargy and distended abdomen. In addition, two males from the high dose group had watery discharge from one eye. One high dose male was found recumbent, showed tremors and was later found dead on Day 2. Small spleens and thymus were observed in 2 low dose mice and all mid-low, mid-high and high dose mice. Distended stomach was observed in 2 mid-low dose mice and in all mid-high and high dose mice. In addition pale liver was observed in all mid-high and high dose mice.

Negative control: 2 % (w/v) sodium salt of carboxymethyl cellulose (low viscosity) in distilled water with Tween 80 (1 mL/L)

Positive control: Cyclophosphamide monohydrate, 40 mg/kg

Study Validity

The vehicle control group had approximately 0.03% micronucleated PCEs and the group mean was comparable to the historical control range. The positive control, cyclophosphamide, induced a statistically significant increase in micronucleated PCEs

as compared to that of the vehicle control, with a mean and standard deviation of 2.20 ± 0.43 .

Results

Mice exhibited treatment related clinical signs of distended abdomen and gross lesions of stomach distended with feed, small thymus and spleen in low and mid dose groups with pale liver in the high dose group. There were no deaths and no effects on body weights noted in this study.

Desoximetasone did not induce a significant increase in micronucleated PCEs in this study. The ratio of PCE: total erythrocytes in both sexes were significantly reduced (10-12%) in mid and high dose groups as compared to vehicle control group indicating bone marrow toxicity of the test article.

Group & Dose (mg/kg)	No. of Mice	To determine PCE: Total RBC ratio			Total *	No. with MN	PCE	
		No. of RBC	No. of PCE	Ratio (Mean)			Total	Mean
G1 0	10	2173	1084	<u>Combined sex</u> 0.50 ± 0.02	21157	7	Total Mean SD	0.03 0.03 0.04
G2 @ 40	10	2305	974	- 0.42 ± 0.02	20793	457	Total Mean SD	2.2 2.20 0.43
G3 300	10	2249	1051	- 0.47 ± 0.01	20910	7	Total Mean SD	0.03 0.03 0.03
G4 600	10	2279	1033	- 0.45 ± 0.01	21982	8	Total Mean SD	0.04 0.04 0.03
G5 1200	10	2290	1017	- 0.44 ± 0.01	21080	9	Total Mean SD	0.04 0.04 0.04

* : Including PCEs counted to determine PCE : Total RBC ratio @:Positive control

+/- : Significantly higher/lower than the control group by Dunnett's test ($p \leq 0.05$)

7.4 Other Genetic Toxicity Studies

N/A

8 Carcinogenicity

No carcinogenicity study was submitted under this NDA. The sponsor committed to conduct a 2 year dermal carcinogenicity study in rats as a post-marketing requirement.

The Sponsor submitted a timeline in response to the 74 day letter sent on September 28, 2012. The proposed timeline is provided in the following table.

Submission of Final Study Protocol (after completion of dose range-finding studies and CAC review)	30 April 2015
Completion of 2-year rat study (in-life)	31 May 2017
Submission of Final Study Report	31 May 2018

Reviewer's comment: The proposed timeline appears acceptable from a pharmacology/toxicology perspective.

9 Reproductive and Developmental Toxicology

The following reproductive and developmental toxicology information was included in desoximetasone cream USP, 0.25% label.

Pregnancy

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

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration in doses 3 to 30 times the human dose of Topicort (desoximetasone cream USP) 0.25% and 15 to 150 times the human dose of Topicort (desoximetasone cream USP) 0.05%, or Topicort (desoximetasone gel USP) 0.05%.

There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, Topicort (desoximetasone) Spray, 0.25% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Information addressing the effect of desoximetasone on fertility was identified by the sponsor during the course of reviewing the older study reports. The sponsor submitted a study that evaluated the effects of desoximetasone on fertility and this study is reviewed below.

9.1 Fertility and Early Embryonic Development

Study title: Effect of Subcutaneous Injections of Compound HOE 304 as

Compared to dexamethasone on the Fertility, Pregnancy and Postnatal development of Rats

Study no.: Experiment 0575-54
 Study report location: Electronic submission, SDN 1
 Conducting laboratory and location: (b) (4)
 Date of study initiation: N/A. Completed 09-01-1975
 GLP compliance: N/A
 QA statement: N/A
 Drug, lot #, and % purity: Compound Hoe 304, lot# RW-1711
 Dexamethasone, lot# RW-2047

Key Study Findings

No evidence of impairment of fertility was observed in male and female Sprague-Dawley rats at subcutaneous doses up to 0.1 mg/kg/day desoximetasone. Test article Hoe 304 is a code name for desoximetasone.

Methods

Doses: 0 (vehicle control), 25 g/kg/day Hoe 304, 100 g/kg/day Hoe 304, and 100 g/kg/day dexamethasone

Frequency of dosing: Once daily, 5 days per week during the pre mating period and 7 days per week from mating and thereafter. *(Reviewer's comment: typically test article administration for fertility studies is 7 days/week during the pre mating period and mating period. However, since this is an older study which does provide some useful information concerning the effects of desoximetasone on fertility, the sponsor will not be asked to repeat this study.)*

Dose volume: N/A

Route of administration: Subcutaneous injection

Formulation/Vehicle: Suspended in propylene glycol at a concentration of 0.0125% during the pre mating period and suspended at a concentration of 2% in carboxymethylcellulose subsequently

Species/Strain: Rat/Sprague-Dawley (CD) rat

Number/Sex/Group: 12 females/Group, 24 males/Group

Satellite groups: None

Study design: After 20 and 61 days of injection of compounds for females and males, respectively, the procedures were as follows (within the respective groups):

1. Injection of compound was continued daily throughout the test.
2. The females were exposed for mating to males for 4 weeks. Copulation was determined by daily vaginal inspection for sperm. A positive finding was considered Day 1 of pregnancy.
3. Six to 8 females from each of the 4 groups who showed signs of pregnancy were Cesarean sectioned about the 13th day of gestation. They were examined for number and distribution of embryos in each uterine horn, presence of empty implantation sites, and embryos undergoing resorption.
4. The remaining pregnant females were allowed to litter normally. The duration of gestation was calculated and the litters examined as soon as possible after delivery for litter size, stillborn, live born and gross anomalies. The pups were sexed and weighed individually at delivery. Any dead pups or those that subsequently died were processed in alcohol, stained with alizarin red, and examined for skeletal defects. The pups were weighed and counted again on Day 4 and Day 21. On the fourth day after delivery, administration of compound was discontinued in the dam and initiated in the pups. Each pup received the compound in the same manner, concentration and dosage as its dam. The amounts were computed according to the average litter weight taken on Days 4 and 10-12.
6. Females which had not conceived earlier were again placed with the same males for 1 week. If this mating was non-productive, then the females were mated with known fertile males.

Deviation from study protocol: No deviations of significance were indicated in this study.

Observations and Results

Mortality

No maternal mortality was observed in this study.

Clinical Signs

During the pre mating period, inflammation followed by ulceration and alopecia developed at the injection sites in all groups of rats. Therefore, the vehicle was changed to a 2% carboxymethylcellulose solution just prior to mating and this vehicle was used for the remainder of the study. The lesions at the treatment site disappeared after the change in vehicle.

Body Weight

Body weight gain was significantly depressed in Groups III and IV males (100 µg/kg Hoe 304 and 100 µg/kg dexamethasone) after one week of dosing. This difference, which was greater in the dexamethasone group and continued throughout the pre mating period. Body weight gain in Group II males (25 µg/kg Hoe 304) was significantly lower after 7 weeks of dosing and thereafter. Body weight gain was significantly depressed during the 2nd and 3rd weeks of pre mating in all groups of corticosteroid treated females.

Feed Consumption

Food consumption of males and females were similar among groups relative to body weights.

Toxicokinetics

N/A

Dosing Solution Analysis

N/A

Necropsy

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Fertility

The fertility rates of male and female rats are summarized in the table below. No significant differences in rates were observed.

Parameter	I	II	III	IV
	Control	25 µg/kg Hoe 304	100 µg/kg Hoe 304	100 µg/kg Dexamethasone
No. of females bred/conceived	24/21	24/23	24/23	24/23
Female fertility index (FI)	87.5%	95.8%	95.8%	95.8%
No. of males mated/fertile	12/12	12/11	12/11	12/12
Male fertility index (FI)	100%	91.7%	91.7%	100%

Treatment related effects on sperm were not evaluated in this study. In addition, histopathological analysis of the male and female reproductive organs was not performed in this study.

Pregnancy and Postnatal Development

The results of laparotomies at 13 to 16 days post/coitum and examination of the uterine contents of impregnated rats from each of the 4 groups are summarized in the table below. There was a higher number of resorptions in Group IV (100 µg/kg dexamethasone) as compared to the other groups.

Parameter	I Control	II 25 µg/kg Hoe 304	III 100 µg/kg Hoe 304	IV 100 µg/kg Dexamethasone
No. of females sacrificed/ pregnant (13/16 days post/ coitum)	6/5	8/8	6/5	8/7
Total number of: implantations	66	119	67	125
resorptions (% occurrence)	2 (3.0)	3 (2.5)	8 (11.9)	22 (17.6)
viable embryos (% occurrence)	64 (97)	116 (97.5)	59 (88.1)	103 (82.4)

The results of the reproductive aspects and the fate of offspring from groups of females allowed to deliver normally are summarized in the table below. There was a higher number of pups dying from birth to weaning in Group IV (100 µg/kg dexamethasone) as compared to the other groups. This is shown by the lower survival and lactation indices.

Dose-dependent lower birth weights of pups as compared to controls were observed. The dexamethasone group was significantly lower than all other groups and continued to remain lower at 4 and 21 days of age. No other significant differences in the reproductive parameters were observed.

Parameter	I	II	III	IV
	Control	25 µg/kg HOE 304	100 µg/kg HOE 304	100 µg/kg Dexamethasone
No. of females allowed to deliver/pregnant	18/16	16/15	18/18	16/16
No. of females with total resorptions	0	0	0	0
Average gestation time (days)	21.4	21.9	21.9	22.0
No. of females died during delivery	0	0	0	0
Dead fetuses (% occurrence)	4 (2.0)	1 (0.5)	2 (0.9)	5 (2.9)
Viable fetuses (% occurrence)	200 (98.0)	184 (99.5)	219 (99.1)	165 (97.1)
Mean litter size at birth (no.)	12.7	12.3	12.3	11.3
Sex ratio (% ♂/♀)	52/48	44/56	40/60	44/56
Survival index:				
from 1-4 days ¹	95.8	92.5	90.6	79.4
from 5-21 days ²	93.2	99.1	95.7	75.9
Lactation index ³	89.6	91.6	87.1	71.9
Mean weights(g):				
at birth	6.0	5.6	5.2*	4.8**
at 4 days ⁴	8.9	8.7	8.1	6.5**
at 21 days-♂	43.7	44.6	43.5	35.5**
-♀	41.2	43.1	42.3	33.0**

1. No. of pups alive at 4 days/No. pups alive at birth x 100.
2. No. pups alive at 21 days/No. pups alive at 5 days x 100.
3. No. pups weaned/No. pups alive at birth x 100.
4. Injections initiated in pups.

Morphology of Offspring

The results of the gross examination of the offspring and the skeletal examination of those that died are summarized in the following table. Of the 779 offspring examined, all were grossly normal. Of the 29 skeletal examinations of dead offspring, only 2 pups showed minor defects (non-significant: bipartite centrum of a cervical vertebra).

Morphology	I Control	II 25 µg/kg Hoe 304	III 100 µg/kg Hoe 304	IV 100 µg/kg Dexamethasone
Gross observations:				
Total number of pups examined	204	185	221	169
Defects:	0	0	0	0
Skeletal observations:				
Total number of dead pups examined ¹	8	3	9	9
Defects: 1. One cervical vertebra with bipartite centrum	2	0	0	0

1. The number of animals examined here does not correspond to the actual number that died, since many were cannibalized.

10 Special Toxicology Studies

Desoximetasone Spray, 0.25% did not elicit overt irritation at the treatment site in the 28 day dermal minipig toxicity study (Study No. 60428, see Section 6.2 for the details).

11 Integrated Summary and Safety Evaluation

The sponsor submitted a 505(b)(1) NDA application for desoximetasone spray, 0.25%, a new dosage form, which is indicated for the relief of moderate to severe plaque psoriasis in patients 18 years of age or older.

Desoximetasone, first approved in the United States in 1977 as Topicort[®], is a synthetic corticosteroid already marketed in a number of formulations: gel (0.05%), cream (0.05% and 0.25%), and ointment (0.05% and 0.25%). The sponsor acquired the Topicort[®] brand in 2003 and has ownership of all the nonclinical toxicology data contained in NDAs 17856, 18763, and 18568 for the various desoximetasone topical formulations to support this NDA.

The toxicity profile of desoximetasone is similar to other corticosteroids. The following local adverse reactions have been noted clinically with the use of topical corticosteroids: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae and malaria. Systemic absorption of topical corticosteroids has produced HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia and glucosuria in some patients.

The sponsor conducted a 28 day repeat dose dermal toxicity bridging study in Göttingen minipigs. Following 28 days of dermal administration of desoximetasone spray, 0.25% and desoximetasone cream, 0.25% to Göttingen minipigs at the same daily dose level of 0.33 mg/kg, no significant differences in toxicological profile were revealed. The signs of toxicity observed were decreases in adrenal weights and reversible atrophic changes in the adrenal gland and/or thymus, which were present in all treated groups. These observations are consistent with results from previous repeat dose toxicity studies and are known pharmacological effects of desoximetasone, resulting from the HPA axis suppression. Although no thymic atrophy was noted following cream administration,

only one of the animals treated at the same dose level with the spray showed this finding. Administration of the spray formulation at a dose level of 1.00 mg/kg/day did reveal a higher incidence of changes in parameters measured in the study compared to lower dose level treated groups. Signs of application site irritation were no more frequent in desoximetasone treated groups than in vehicle control group.

Toxicokinetic analysis demonstrated that dermal administration of desoximetasone spray, 0.25% resulted in greater systemic exposure to active drug than desoximetasone cream, 0.25% (C_{max} and AUC_{0-24} values were approximately 2-fold greater for the spray formulation). However, as the extent of absorption is minimal, this difference is not toxicologically significant. There are no clear gender differences in TK parameters within a dose or formulation.

The sponsor also submitted an ICH standard battery of genetic toxicology. Desoximetasone revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster ovary cell chromosome aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Long-term animal studies have not been performed to evaluate the carcinogenic potential of topical corticosteroids. The sponsor committed to conduct a 2 year dermal carcinogenicity study in rats as a post-marketing requirement. The timeline the sponsor submitted appears acceptable.

No evidence of impairment of fertility was observed in male and female Sprague-Dawley rats at subcutaneous doses up to 0.1 mg/kg/day desoximetasone.

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

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration in doses 3 to 30 times the human dose of Topicort (desoximetasone cream USP) 0.25% and 15 to 150 times the human dose of Topicort (desoximetasone cream USP) 0.05%, or Topicort (desoximetasone gel USP) 0.05%.

Desoximetasone spray, 0.25% does not contain any novel excipients. None of the impurities in the drug substance are above the ICH qualification threshold. Impurities (b) (4) in the proposed drug product are above the ICH qualification threshold. However, there are no concerns from a pharmacology/toxicology perspective based on the nonclinical data and justification the sponsor provided.

12 Appendix/Attachments

N/A

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

/s/

Renqin DUAN
01/07/2013

BARBARA A HILL
01/07/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204141

Applicant: Taro Pharmaceuticals
USA Inc

Stamp Date: 06-12-2012

Drug Name: Topicort
(desoximetasone) Spray, 0.25%

NDA Type: Original-505(b)(1)

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?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
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)?	X		The sponsor has ownership of all the nonclinical toxicology data contained in NDAs 17856, 18763, and 18568 to support this NDA, which makes this a 505(b)(1) NDA. Based on the agreement between the Agency and the sponsor, the carcinogenic potential of the drug product will be evaluated in rats post approval of the NDA. The sponsor should provide the timeline for conduct of the carcinogenicity study as a post-marketing requirement.
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).	X		
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 <u>submitted</u> a rationale to justify the alternative route?	X		

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

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The labeling may need to be revised.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

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

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

You should provide the timeline for conduct of your carcinogenicity study as a post-marketing requirement and specify the date you will submit the final study protocol, complete the study and submit the final study report.

Renqin Duan, PhD 07-16-2012

 Reviewing Pharmacologist Date

Barbara Hill, PhD See sign off date

 Supervisor Date

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

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/s/

Renqin DUAN
07/23/2012

BARBARA A HILL
07/23/2012