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APPLICATION NUMBER:

21-835

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA	21-835
Submission Date	12/22/2004, 3/8/2005, 7/22/2005
Brand Name	Clobex™
Generic Name	Clobetasol Propionate
Reviewer	Lei Zhang, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III
OND Division	DDDDP (HFD-540)
Applicant	Dow Pharmaceutical Sciences
Relevant IND	IND 62,543
Type of Submission; Code	505 (b)(1); 3S
Formulation; Strength(s)	Spray; 0.05%
Indication	Treatment of moderate to severe plaque psoriasis in patients 18 years and older

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1 EXECUTIVE SUMMARY

Clobetasol propionate is a synthetic fluorinated corticosteroid used topically for its anti-inflammatory and anti-pruritic properties. It is currently marketed in various formulations that include cream, ointment, gel, emollient cream, solution, lotion, scalp application, foam, and shampoo for short-term topical treatment of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses. The relevant NDAs for clobetasol topical use, are listed below (from earliest to latest submission).

- NDA 19-322 Temovate (Clobetasol propionate 0.05%) Topical Cream -Glaxo
- NDA 19-323 Temovate (Clobetasol propionate 0.05%) Topical Ointment -Glaxo
- NDA 19-966 Temovate (Clobetasol propionate 0.05%) Topical Solution -Glaxo
- NDA 19-966 Temovate (Clobetasol propionate 0.05%) Topical Scalp application -Glaxo
- NDA 19-340 Temovate (Clobetasol propionate 0.05%) Topical Emollient Cream -Glaxo
- NDA 19-337 Temovate (Clobetasol propionate 0.05%) Topical Gel –Glaxo
- NDA 21-535 CLOBEX (Clobetasol propionate 0.05%) Topical Lotion –Galderma
- NDA 21-644 CLOBEX (Clobetasol propionate 0.05%) Topical Shampoo –Galderma

The subject of this 505 (b)(1) NDA application, CLOBEX™ (clobetasol propionate) Spray, 0.05%, represents a new formulation to be indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years or older. It is proposed by the Sponsor that the spray formulation offers a unique dosage form delivered via a pump with a known delivery volume which could provide the prescribing physician and patient improved control of the quantity of drug applied compared to the currently available treatment modalities. The proposed spray formulation also offers cosmetic advantages over ointments and creams in that it is less greasy and is easier to apply.

To support Clinical Pharmacology and Biopharmaceutics requirement for this NDA, the Sponsor used pharmacodynamic endpoints of topical vasoconstriction and hypothalamic-pituitary-adrenal (HPA) axis testing.

The vasoconstrictor study (Study TI00-01003) results indicated that 0.05% clobetasol propionate spray is a super-high potency topical corticosteroid. As of note, previous 0.05% clobetasol propionate products (various formulations) are also classified as super-high potency topical corticosteroids.

The Sponsor evaluated HPA axis function (Study TI01-01009 and Study D02-0204-03) in adult patients with moderate to severe plaque-type psoriasis (≥ 20% BSA) from the application of CLOBEX™ 0.05% spray twice daily for 2 or 4 weeks in clinical investigations.

The efficacy and safety of CLOBEX™ (clobetasol propionate) Spray, 0.05% in psoriasis has been studied in two pivotal, adequate and well-controlled clinical trials (Studies TI01-01008 and TI01-01010), which were identical in design. The studies were conducted in a total of 240 patients with moderate to severe plaque psoriasis. Patients were treated twice daily for 4 weeks with either CLOBEX™ (clobetasol propionate) Spray, 0.05% or vehicle spray. Please refer to Dr. Denise Cook's review for detailed results of efficacy and safety evaluation for CLOBEX™ (clobetasol propionate) Spray, 0.05%.

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, this application is acceptable. Recommendations for consideration for the final labeling are included in Section 3.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

In the current submission, the following studies were submitted to support Human Pharmacokinetics and Bioavailability section:

Vasoconstrictor Assay in Healthy Subjects

Study TI00-01003 was designed to evaluate the topical potency of clobetasol propionate spray (CPS), 0.05% for its vasoconstrictor effect in comparison to the currently marketed topical corticosteroids [Temovate E® Emollient Cream (clobetasol propionate 0.05%, Elan Pharmaceuticals) (TEEC), Cyclocort Cream® (amcinonide 0.1%, Fujisawa Healthcare Inc.) (CC)], and the vehicle for CPS. Both visual scoring method (primary) and chromametric measurement (secondary) were used to assess the potency.

The primary visual scoring efficacy data demonstrates vasoconstrictive properties of CPS which are equivalent to the reference group I corticosteroid (TEEC) as well as being more potent than the reference drug of lower potency (CC).

The secondary chromametric measurement efficacy data demonstrated that CPS has similar potency as CC and both are less potent than TEEC. While the rank ordering between the reference products are reproducible by the two methods (visual scoring and chromametric measurement), the rank ordering of the potency of the test product differs between the two methods.

The CPS product was classified as a super-high potent corticosteroid based on visual scoring.

Adrenal Suppression Studies in Clinical Subjects

The Sponsor evaluated HPA axis function (Study TI01-01009 and Study D02-0204-03) in adult patients with moderate to severe plaque-type psoriasis (≥ 20% BSA) following the application of CLOBEX™ 0.05% spray twice daily for 2 or 4 weeks in clinical investigations. The results showed that 2 out of 13 subjects (15%) and 3 out of 15 subjects (20%) had HPA axis suppression at the end of 4-week treatment from Study TI01-01009 and Study D02-0204-03, respectively. Similar percentage of subjects showed HPA axis suppression (4 out of 21 subjects, 19%) after 2-week treatment in Study D02-0204-03, suggesting that HPA axis suppression is produced rapidly in susceptible individuals.

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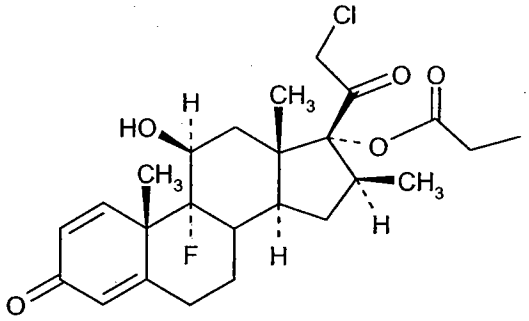
2 QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What are the highlights of the physicochemical properties of clobetasol propionate?

Table 2.1.1.1. Physical-Chemical Properties of Clobetasol Propionate

Drug Name	Clobetasol Propionate
Chemical Name	21-chloro-9-fluoro-11β,17-dihydroxy-16β -methylpregna-1,4-diene-3,20-dione17-propionate
Structure and Molecular Formula	 $C_{25}H_{32}ClFO_5$
Molecular Weight	466.97
Appearance	White or almost white crystalline powder
Melting Range	Approximately [redacted]
Solubility	Soluble in acetone, chloroform, and dioxane; sparingly soluble in methanol; insoluble in water

2.1.2. What are the proposed therapeutic indication, dosage, route of administration, and mechanism of action of clobetasol propionate spray, 0.05% from the Sponsor?

Proposed Indication:
CLOBEX™ (clobetasol propionate) Spray, 0.05% is indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age or older.

Dosage and Route of Administration:
CLOBEX™ (clobetasol propionate) Spray, 0.05% should be applied topically to the affected skin areas twice daily and rubbed in gently and completely.

CLOBEX™ (clobetasol propionate) Spray, 0.05% contains a super-high potent topical corticosteroid; therefore treatment should be limited to 4 weeks. The total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Mechanism of Action:
Like other topical corticosteroids CLOBEX™ (clobetasol propionate) Spray, 0.05% has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids in general is unclear. However, corticosteroids are thought to act by induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

2.2. General Clinical Pharmacology

2.2.1. What studies have been conducted for biopharmaceutic/bioavailability evaluation of the drug product? What are the outcomes of these studies?

Complete study reports for one vasoconstrictor studies (Study TI00-01003) and two HPA axis studies (Study TI01-01009 and Study D02-0204-03) were included in the submission.

Results of Vasoconstriction Study:
Study TI00-01003 was designed to evaluate the topical potency of clobetasol propionate spray (CPS), 0.05% for its vasoconstrictor effect in comparison to the currently marketed topical corticosteroids [Temovate E® Emollient Cream (clobetasol propionate 0.05%, Elan Pharmaceuticals) (TEEC), Cyclocort Cream® (amcinonide 0.1%, Fujisawa Healthcare Inc.) (CC)], and the vehicle for CPS. Both visual scoring method (primary) and chromametric measurement (secondary) were used to assess the potency.

The primary visual scoring efficacy data demonstrates vasoconstrictive properties of CPS which are equivalent to the reference group I corticosteroid (TEEC) as well as being more potent than the reference drug of lower potency (CC) (Figure 2.2.1.1).

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Results of HPA Axis Suppression Studies:

The Sponsor evaluated HPA axis function (Study TI01-01009 and Study D02-0204-03) in adult patients with moderate to severe plaque-type psoriasis (≥ 20% BSA) from the application of CLOBEX™ 0.05% spray twice daily for 2 or 4 weeks in clinical investigations.

1) Study No. TI01-01009: An Open Label, Non-Comparative Evaluation of the Adrenal Suppression Potential of Clobetasol Propionate 0.05% Spray in Subjects with Plaque Psoriasis.

   16 patients with moderate to severe plaque psoriasis (≥ 20% BSA) were enrolled. (≤ 3.5 g) of test material was applied twice daily for 4 weeks (1 mg/cm^2) to each subject.

   Results: 14 subjects completed the study and 13 subjects were evaluable for HPA axis suppression. Mean baseline BSA value for these 13 subjects was 36 ± 20% (range [redacted] Based on 30-min post-stimulation criterion (level ≤ 18 µg/dL) for HPA axis suppression, 2 out of 13 subjects (15%) were suppressed at the end of 4-week treatment.

2) Study No. D02-0204-03: An Open Label, Non-Comparative Evaluation of the Adrenal Suppression Potential of Clobetasol Propionate 0.05% Spray in Subjects with Moderate to Severe Plaque Psoriasis: Two and Four Week Treatment.

   41 patients with moderate to severe plaque psoriasis (≥ 20% BSA) were enrolled. (≤ 3.5 g) of test material was applied twice daily for 2 or 4 weeks (maximum 7 g per day).

   Results: 19 subjects in the 2-week group completed the study and 17 subjects in the 4-week group completed the study. Two subjects in the 4-week treatment group completed the study at Week 2 due to complete clearing and they were included to the 2-week treatment group for HPA axis function assessment.

   ***For the 2-week group:** 21 subjects in the 2-week treatment group were evaluable for HPA axis suppression. Mean baseline BSA value for these 21 subjects was 21 ± 2% (range [redacted] Based on 1 criterion, 4/21 (19%) was suppressed.*

   ***For the 4-week group:** 15 subjects in the 4-week treatment group were evaluable for HPA axis suppression. Mean baseline BSA value for these 15 subjects was 21 ± 2% (range [redacted] Based on the 30min post-stimulation criterion, 3/15 (20%) were suppressed.*

HPA axis suppression summary (based on 30-min post-stimulation level ≤ 18 µg/dL)

	Study TI01-01009	Study D02-0204-03
2-week	-	4/21 (19%)
4-week	2/13 (15%)	3/15 (20%)

Reviewer's Note: Although subjects in the HPA axis study met the inclusion criteria with baseline %BSA ≥ 20%, majority of the patients had 20% BSA.

2.5 General Biopharmaceutics

2.5.1. What is formulation (quantitative composition) of 0.05% CLOBEX (clobetasol propionate) spray?

The finished product, CLOBEX™ (clobetasol propionate) Spray, 0.05% is a clear, colorless alcoholic solution (spray) for topical use to treat psoriasis. It contains Clobetasol Propionate, USP, at the strength of 0.05% (0.5 mg/g). Table 2.5.1.1 shows the composition of the drug product.

Table 2.5.1.1. Quantitative Composition of CLOBEX™ (clobetasol propionate) Spray, 0.05%.

Component	Function	Percent (w/w)
Clobetasol Propionate	Active Ingredient	0.05
Ethanol *		
Water *		
Isopropyl Myristate		
Sodium Lauryl Sulfate		
Undecylenic Acid		

* Added as Alcohol, USP which contains approximately

CLOBEX™ (clobetasol propionate) Spray, 0.05% is filled into a 2-oz high density polyethylene (HDPE) bottle with a polypropylene cap. The product will be dispensed from the bottle using a non-aerosol spray pump. A dose of approximately 0.14 mL per actuation
containing of clobetasol propionate) is delivered from the non-aerosol spray pump.

2.5.2. Are there any differences between clinical and to-be-marketed formulations?

No. Because various batch numbers/reference numbers were listed in the study reports and detailed formulation composition information was not available, an information request was sent to the sponsor regarding the formulations used in the clinical studies. The Sponsor confirmed that the to-be-marketed formulation was used in all clinical studies, including the HPA axis studies.

The Table below lists study drug batch numbers for all Clobex™ Clinical Studies.

Study ID and Type of Study	Batch Number of Study Drug	Additional Reference Number	Batch Size
TI01-01008 Phase 3 Efficacy	**669**	010604	
TI01-01010 Phase 3 Efficacy	**669**	010803	
D02-0204-03 Phase 2 Safety (HPA)	**859**	500199	

Study ID and Type of Study	Batch Number of Study Drug	Additional Reference Number	Batch Size
TI01-01009 Phase 2 Safety (HPA)	**639** - Subjects 1-9 **670** - Subjects 10-16	None 696	[redacted]
TI00-01003 Phase 2 Safety (VCA)	**639**	None	
0215-C1.P-01-01 Phase 1 Safety and Efficacy	**639**	None	
TI01-01004 Phase 1 Safety (21-Day Cum.)	**639**	None	
TI01-01005 Phase 1 Safety (Repeat Insult Patch Test)	**639**	None	
TI01-01006 Phase 1 Safety (Phototoxicity)	**639**	None	
TI01-01007 Phase 1 Safety (Photocontact Allergy)	**639**	None	

3 DETAILED LABELING RECOMMENDATIONS

Recommendations for changes to the proposed labeling are provided below (only affected sections relating to Clinical Pharmacology are listed). Please refer to the final approval letter for the final version of the approved labeling.

CLINICAL PHARMACOLOGY:

[redacted]

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4.2 Individual Study Reviews

4.2.1 Vasoconstrictor Study

4.2.1.1. *Study TI00-01003: A Randomized, Evaluator Blinded, within Subject, Single-Center Evaluation of the Vasoconstrictive Properties of Clobetasol Propionate Spray 0.05%, in Normal Healthy Volunteers*

Study Rationale: Topical corticosteroids produce a localized skin-blanching response when applied to skin, caused by constriction of the superficial blood vessels of the skin. The degree of skin blanching assessed by visual scoring is a measure of the inherent potency of the drug and its capacity to diffuse through the stratum corneum. The vasoconstrictor assay is the most widely used surrogate test to assess the potency of topical corticosteroids.

Objectives: To demonstrate the relative vasoconstrictive potential of clobetasol propionate 0.05% spray (CPS) compared to Temovate E® Emollient Cream (clobetasol propionate 0.05%, Elan Pharmaceuticals) (TEEC), Cyclocort Cream® (amcinonide 0.1%, Fujisawa Healthcare Inc.) (CC), and the vehicle for CPS.

Study Site: [redacted]

Investigator: [redacted]

Study Period: June 27, 2002 to July 31, 2002

Study Design: This was a 2-day, randomized, evaluator-blinded, within-subject, single-center study. Thirty-six healthy volunteers (21-56 Years, 9 males and 27 females) enrolled and completed the study (Table 4.2.1.1.1). Subjects without a history of documented vasoconstriction to topical corticosteroids were screened by placing ~ 10 mg of a moderate potency corticosteroid (Cutivate® ointment, fluticasone propionate 0.005%, Elan Pharmaceuticals) on the left upper arm and covering it with a protective non-occlusive guard affixed with tape. The following day, the guard was removed and the site evaluated for vasoconstriction. Subjects demonstrating vasoconstriction during this screening evaluation were allowed to enroll in the study.

On Day 1, each subject had three 1 cm^2 test sites identified on each ventral forearm. Baseline chromametric readings were taken from these sites using a [redacted] Chromameter [redacted]. A single application of approximately 10 µL of each study medication was applied later in the afternoon (approximately 4 pm) in accordance with a computer-generated randomization code. Four different study medications were evaluated, one test site was left as a chromametric control and the final site (randomly assigned) was not used. Test sites were protected using a raised, perforated guard that was secured to the arm with nonocclusive tape. Subjects were instructed to keep the test sites dry, and were scheduled to return the following day.

On Day 2, 16 hours following study medication applications, the subjects removed the protective guards and gently washed the test sites with mild soap and water. Upon return to the clinic, 2

hours later (18 hours after the study medication applications), an experienced evaluator performed the Visual Assessment of Vasoconstriction (skin-blanching) and assessed the skin at each site based on a 4-point scale (0-3):
0 = no blanching
1 = mild blanching
2 = moderate blanching
3 = marked blanching

Chromametric readings were also performed at each test site.

Duration of treatment: 16 hours

Subjects: 36 healthy subjects

Table 4.2.1.1.1. Summary of Demographics.

Sex	Males	9	25.0%
	Females	27	75.0%
Age	Minimum age =	21.3 years	
	Maximum age =	56.4 years	
	Average Age	39.4 years	
Race	Caucasian	28	77.8%
	Hispanic	3	8.3%
	Afro-American	0	0.0%
	Asian	4	11.1%
	Other	1	2.8%

Investigational product:
Clobetasol propionate 0.05% in spray formulation, Lot number – 639

Comparator:
1) Temovate E® Emollient Cream (clobetasol propionate cream 0.05%), Lot number – 1A285
2) Cyclocort® Cream (amcinonide 0.1%), Lot number – PIHN-1

3) Vehicle Spray, Lot number – 649

Criteria for evaluation:
Efficacy:
Primary – Vasoconstriction visual scores equivalent to reference products
Secondary – Corrected changes in chromametric values equivalent to reference products

Safety: Numbers and severity of adverse events

Statistical Analysis and Data Handling:
Because this was a within-subject design, skin-blanching and the corrected chromametric measure 'a' (red-green balance) were analyzed for mean differences among treatments using a randomized blocks analysis of variance (using ranked data for the visual assessment analysis). The blocking variable was the subject. Within this analysis of variance, the mean ranked visual assessment score for each study medication was compared using the [redacted]. All statistical analyses used a 0.05 alpha value (two-tailed).

Results:
Visual Assessments:
Total vasoconstriction scores ranged from 17 (placebo) through 89 (CPS) (Figure 4.2.1.1.1), with mean scores ranging from '0.47' (0 = no blanching) at the placebo treatment site to '2.5' (3 = marked blanching) at the CPS treatment site (Table 4.2.1.1.2). Per the [redacted], all active study medications demonstrated significantly greater changes in skin blanching than the CPS vehicle. CPS and TEEC values were very similar and did not show a statistically significant difference from one another. Both of these clobetasol propionate formulations were statistically more vasoconstrictive than CC.

Table 4.2.1.1.2. Summary of Visual Assessments of Vasoconstriction.

Code	Product	Potency	Mean Score
A	Clobetasol Propionate Spray, 0.05% (CPS)	Test	2.5 ± 0.65
B	CPS Vehicle	Negative Control	0.47 ± 0.81
C	Temovate E® Emollient Cream (clobetasol propionate cream,0.05%)	Super-High	2.47 ± 0.74
D	Cyclocort® Cream (amcinonide 0.1%)	High	1.61 ± 1.08

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Discussion and Conclusions:
The primary visual scoring efficacy data demonstrates vasoconstrictive properties of CPS which are equivalent to the reference group I corticosteroid (TEEC) as well as being more potent than the reference drug of lower potency (CC).

The secondary chromametric measurement efficacy data demonstrated that CPS has similar potency as CC and both are less potent than TEEC. While the rank ordering between the reference products are reproducible by the two methods (visual scoring and chromametric measurement), the rank ordering of the potency of the test product differs between the two methods.

The visual scoring method ranks CPS as a super-high potent corticosteroid.

4.2.2 HPA Axis Suppression Study

4.2.2.1. Study TI01-01009: An Open Label, Non-Comparative Evaluation of the Adrenal Suppression Potential of Clobetasol Propionate 0.05% Spray in Subjects with Plaque Psoriasis

Objectives: To evaluate the safety and adrenal suppression potential of the intended market formulation of a clobetasol propionate 0.05% spray in the treatment of subjects with plaque psoriasis.

(Reviewer's Note: In the protocol and study report, the Sponsor defined normal HPA axis function as 1) an early morning serum cortisol level >5 µg/dL, 2) serum cortisol levels >18 µg/dL approximately 30 minutes following stimulation, and 3) with an increase over basal levels ≥ 7 µg/dL, in response to 0.25 mg cosyntropin administered by intravenous (IV) injection. In the FDA draft guidance, only one criterion, i.e., serum cortisol level > 18 µg/dL 30-min post-stimulation is recommended as the indication for normal HPA axis function. Therefore, the Reviewer used a 30-min post-stimulation level ≤ 18 µg/dL as the definition for HPA axis suppression to review the HPA axis data for this study.)

Study Sites: Two study sites in the U.S.

Investigators: [redacted]

Study Period: September 11, 2001 to March 19, 2002

Study Design: This was a multiple center, open label, non-comparative study of the intended market formulation of clobetasol propionate 0.05% spray in subjects with moderate to severe

plaque psoriasis. Approximately sixteen subjects with at least moderate to severe plaque psoriasis on at least 20% of their body surface area (excluding the face, scalp, groin, axillae and other intertriginous areas) who fulfilled the inclusion/exclusion criteria were enrolled at multiple US study sites. Subjects applied the study medication (the intended market formulation of clobetasol propionate 0.05% spray) to all psoriasis plaques (~1 mg/cm^2) identified at Visit 1 twice daily for 28 days or until the investigator verified the subject's psoriasis had cleared. The maximum applied dose was 7 grams daily (3.5 g BID) for a total of approximately 50 g per week.

All subjects had a cosyntropin stimulation test to assess their HPA response at Visit 1 and at the end of the scheduled 28-day treatment period (or earlier if the investigator verified the subject's psoriasis has cleared). If adrenal suppression was noted, the cosyntropin stimulation test was repeated approximately 1 week later. In addition to the cosyntropin stimulation test, subjects had samples for routine eight-hour fasting hematology, chemistry and urinalysis collected.

If the results of the Visit 1 cosyntropin stimulation test indicated the subject had an abnormal HPA-system response, the subject was withdrawn from the study and the abnormality was reported as an adverse event. In addition, the subject was directed to consult with their physician concerning the abnormality.

If a subject's end of treatment period (Visit 5 or earlier) laboratory results showed an abnormal HPA-system response, the study medication was considered to have caused adrenal suppression in the subject. This situation was reported as an adverse event. The subject was instructed not to use ANY topical or systemic steroids, or any other therapies that may affect plaque psoriasis. The subject was instructed to return for a follow-up visit seven days after the 'end of treatment period' laboratory samples were collected. The subject could continue to use the standard emollient and the investigator approved, medicated (non-steroid) shampoo.

Besides HPA axis assessment, other safety measurements and efficacy information were also collected from the study. This review will focus on HPA axis suppression as indicated by post-stimulation cortisol levels.

Duration of treatment: Twice daily for 4 weeks

Subjects: A total of 16 subjects (20-55 Years, 11 males and 5 females) were enrolled in the study of which 14 subjects completed. Subject 6 (male) discontinued because this subject's cosyntropin stimulation test at Visit was abnormal. Subject 4 (male) completed the dosing phase of the study. However, this subject experienced adverse event shortly after cosyntropin injection on Day 29 and was lost to follow-up. Subject 16 (male) had a two-week delay in the scheduled Visit 5 (Day 29) because of being hospitalized for probable methamphetamine abuse. Because the delay limits any meaningful interpretation of his response to therapy form an adrenal suppression standpoint, this subject would be excluded from the HPA axis suppression assessment. Therefore, a total of 13 subjects were evaluable for HPA axis suppression assessment.

The baseline and demographic characteristics of the 16 subjects enrolled in the study are presented in Table 4.2.2.1.1.

Table 4.2.2.1.1. Summary of Baseline Demographic Characteristics.

Number of Subjects	16
Age (years)	
n	16
Mean	37.75
STD	10.30
Range	20.0 - 55.0
Gender	
Male	11 (69%)
Female	5 (31%)
Race	
White	13 (81%)
Black	0 (0%)
Asian/Pacific Islander	2 (13%)
Hispanic/Latino	1 (6%)
American/Alaskan Native	0 (0%)
Other	0 (0%)
Height (in)	
n	16
Mean	68.25
STD	3.80
Range	59.4 - 72.0
Weight (lb)	
n	16
Mean	220.14
STD	50.70
Range	130.0 - 299.0
BSA	
n	15
Mean	34.6
STD	19.3
Range	20-98

Investigational product:
Drug name: Clobetasol propionate 0.05% spray
Active ingredient: Clobetasol propionate
Other ingredients: Isopropyl myristate, alcohol, undecylenic acid, sodium lauryl sulfate.
Lot Numbers: 639 (Subjects 1-9) and 696 (Subjects 10-16)

Clobetasol propionate 0.05% spray was manufactured, packaged and labeled by Dow Pharmaceutical Sciences, Petaluma, California, USA.

Results:

Each subjects applied the study medication to all psoriatic plaques identified at Visit 1 twice daily for four weeks or until the investigator verified their psoriasis had cleared. Study medication bottles were not weighted during treatment. Mean number of applications for 16 subjects was 50 (range 5-60).

Serum cortisol level data are listed in Table 4.2.2.1.2. As mentioned in the Subject section earlier, Subjects 4, 6 and 16 were excluded from HPA axis function assessment. Based on 1 criterion (30-min post-stimulation level ≤ 18 µg/dL), 2 subjects out of 13 evaluable subjects (15%) were suppressed (Subjects 1 and 9). The HPA axis function for both subjects returned to normal when tested approximately one week off the therapy (Visit 6). %BSA and HPA axis suppression status for each subject are listed in Table 4.2.2.1.3.

Table 4.2.2.1.2. Cosyntropin Stimulation Test Results.

	Visit 2		Visit 5		Visit 6		Days Out	Visit 7		Days Out
Subject	Pre	Post	Pre	Post	Pre	Post	from Visit 5	Pre	Post	from Visit 6
							7 days	N/A	N/A	
							7 days	N/A	N/A	
								N/A	N/A	
								N/A	N/A	
							7 days	N/A	N/A	
								N/A	N/A	
								N/A	N/A	
								N/A	N/A	
							8 days	N/A	N/A	
								N/A	N/A	
							10 days	[redacted]		8 days
								N/A	N/A	
								N/A	N/A	
								N/A	N/A	
								N/A	N/A	
								N/A	N/A	
Mean	14.8	28.4	11.7	22.6	18.8	27.3		24.0	31.0	
N	16	16	15	14	5	5		1	1	

[redacted]
* Suppressed Subjects based on 3 criteria.
** Dropped Subjects
*** Subject 2 had follow on repeat stimulation test Visit 6 in error, as normal function was documented for this subject at the end of the treatment phase, Visit 5.
+ Subject 16 had Visit 5 labs performed approximately 2 weeks [redacted] after drug discontinued on [redacted] due to being hospitalized for a serious adverse event as per Section 12.5.1.
++ Subject 12 received a single intralesional injection during the treatment phase. Although this was a potential confounding factor, it was not likely to be of clinical significance because the subject demonstrated no laboratory evidence of adrenal suppression.

Table 4.2.2.1.3. % BSA and HPA Axis Suppression Status for Subjects in Study TI01-01009.

Subject No.	%BSA at Baseline	HPA axis Suppression at Week 4
1	20	Yes
2	25	No
3	24	No
4	35	Excluded
5	22	No
6	n/a	Excluded
7	45	No
8	42	No
9	98	Yes
10	38	No
11	28	No
12	35	No
13	21	No
14	28	No
15	36	No
16	22	Excluded

The average pre-stimulation cortisol concentration at baseline was 14.79 ± 6.77 µg/dL (mean ± S.D.) and the average post-stimulation cortisol concentration was 28.38 ± 8.10 µg/dL. Following 28 days of treatment, the pre-stimulation cortisol concentration averaged 11.71 ± 7.61 µg/dL and the post-stimulation cortisol concentration averaged 22.61 ± 7.50 µg/dL. There was an average decrease of 3.27 ± 4.48 µg/dL in the pre-stimulation cortisol concentration and an average decrease of 6.94 ± 6.16 µg/dL in the post-stimulation cortisol concentrations following 28 days of treatment.

Discussion and Conclusions:

HPA axis suppression potential of clobetasol propionate spray, 0.05% was evaluated in adult patients with moderate to severe plaque psoriasis (≥ 20% BSA) by applying the medication twice daily for 4 weeks. The maximal usage condition was met as defined by the proposed labeling. In addition, a to-be-marketed formulation of the drug product was used. Under this condition, 2 out of 13 evaluable patients (15%) demonstrated HPA axis suppression at the end of treatment (Week 4). Their HPA axis function returned to normal after one week of discontinuation of therapy.

4.2.2.2 Study D02-0204-03: An Open Label, Non-Comparative Evaluation of the Adrenal Suppression Potential of Clobetasol Propionate 0.05% Spray in Subjects with Moderate to Severe Plaque Psoriasis: Two and Four Week Treatment

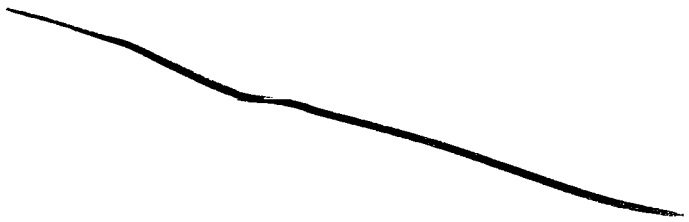
Objectives: The primary objective of this study was to determine the adrenal suppression potential of a new spray formulation of clobetasol propionate 0.05% spray in subjects with moderate to severe plaque psoriasis after twice daily topical dosing for up to 28 consecutive days.

The secondary objective was to determine the change in disease severity during treatment with clobetasol propionate 0.05% spray.

Rationale of the Study: Adrenal suppression effects of topical steroids, especially for those with high potency such as clobetasol propionate 0.05%, is one of the most important safety factors of concern for this group of products. Efficacy data suggests that four weeks of treatment with clobetasol propionate spray, 0.05% is superior to two weeks of treatment. This study was designed to more fully characterize the adrenal effects of the intended market formulation of clobetasol propionate 0.05% in a spray formulation and to ascertain if there is additional risk in four weeks of treatment.

(Reviewer's Note: This review will focus on the HPA axis evaluation as part of the safety evaluation for 0.1% fluocinonide cream. Same as the review for Study TI01-01009, the Reviewer used a 30-min post-stimulation level ≤ 18 μg/dL as the definition for HPA axis suppression.)

Study Sites:



Investigators

Study Period: December 5, 2003 to April 2, 2004

Study Design: This was a multiple center, open label, non-comparative study of the intended market formulation of clobetasol propionate 0.05% spray in subjects with moderate to severe plaque psoriasis. Forty-one subjects with at least moderate to severe plaque psoriasis on at least 20% of their body surface area (excluding the face, scalp, groin, axillae and other intertriginous areas) who fulfilled the inclusion/exclusion criteria were enrolled at multiple US study sites. Subjects were randomized to treatment for either 14 or 28 days. Subjects applied the study medication to all psoriasis plaques identified at Visit 1 twice daily for the assigned treatment period or until the investigator verified the subject's psoriasis had cleared.

The study was designed to determine the adrenal suppression potential of the study medication when the subject applied a maximum of 7 grams daily (3.5 grams twice daily) for a total of approximately 50 grams per week. All subjects had a cosyntropin stimulation test to assess their HPA-system response at Visit 1 and at the end of the scheduled treatment period (or earlier if the investigator verified the subject's psoriasis has cleared).

Besides HPA axis assessment, other safety measurements and efficacy information were also collected from the study. This review will focus on HPA axis suppression as indicated by post-stimulation cortisol levels.

Duration of treatment: 2 weeks or 4 weeks

Subjects: A total of 41 subjects were enrolled in the study of which 21 subjects were randomized to 2 weeks treatment and 20 subjects were randomized to 4 weeks treatment. Two subjects (Subjects 10 and 17) in the 2- week treatment group were dropped subsequent to the first visit due to abnormal baseline serum cortisol levels and/or abnormal baseline HPA-System function (based on 3 criteria for HPA axis suppression used by the Sponsor) and were excluded from the modified-intent-to treat population by the Sponsor. Of the 20 subjects in the 4-week treatment group, 17 subjects completed the study. Two subjects were dropped subsequent to the first visit because 1 subject (Subject 48) had an abnormal baseline serum cortisol levels and/or abnormal baseline HPA-System function (based on 3 criteria for HPA axis suppression used by the Sponsor) and the other subject (Subject 6) had out-of-range and clinically significant baseline laboratory results. One subject (Subject 18) was dropped due to non-compliance (baseline serum samples taken outside the 7:00am to 9:00am timeframe). One subject (Subject 7) requested to withdraw early from the study because based on 3 criteria this subject's HPA axis function was not returned to normal at the time of withdrawal. However, this subject's HPA axis function was returned to normal at the time of withdrawal based on one criterion used by the Reviewer. So this subject was included in the HPA axis assessment. A total of 35 subjects were evaluable for HPA axis suppression assessment (19 who randomized to the 2-week treatment group and 17 who randomized to the 4-week treatment group).

The modified intent-to-treat (MITT) population excluded subjects withdrawn from the study at Visit 2 due to abnormal serum cortisol, abnormal HPA-system function, or out-of-range clinically significant baseline laboratory test results.

In the MITT population, average age of subjects in the 2-week treatment group was 49.06 years and average age of subjects in the 4-week treatment group was 44.31 years (Table 4.2.2.2.1). Fifty-eight percent (11/19) of subjects in the 2-week treatment group were male compared to 88% (15/17) in the 4-week treatment group. Within each treatment group, approximately 80% of subjects were white. Percent BSA in the 2-week treatment group averaged 20.84% compared to 20.71% for subjects in the 4-week treatment group.

Across both treatment groups, approximately 70% of the subjects had moderate scaling (26/36, 72%), plaque elevation (24/36, 67%), and erythema (25/36, 69%) as well as overall disease severity (28/36, 78%). Seventy-eight percent of subjects (32/36) reported moderate to severe/very severe pruritus. None of the subjects in the MITT population showed evidence of adrenal suppression at baseline.

Table 4.2.2.2.1. Subject Demographic and Baseline Characteristics (Modified Intent-to-Treat Subjects).

	2 Weeks	4 Weeks
Number of Subjects	19	17
Age (years)		
Mean	49.06	44.31
Std	12.32	11.49
Range	24.6-66.0	22.4-61.3
Gender		
Male	11 (58%)	15 (88%)
Female	8 (42%)	2 (12%)
Race		
White	15 (79%)	14 (82%)
Black	1 (5%)	0 (0%)
Asian/Pacific Islander	0 (0%)	1 (6%)
Hispanic/Latino	2 (11%)	1 (6%)
American/Alaskan Native	1 (5%)	1 (6%)
Other	0 (0%)	0 (0%)
Height (in)		
Mean	67.68	69.53
Std	3.72	3.04
Range	62.0-75.0	64.0-75.0
Weight (lb)		
Mean	204.68	220.21
Std	57.45	54.10
Range	130.0-334.0	150.0-326.0
%BSA		
Mean	20.84	20.71
Std	2.54	2.20
Range	20.0-31.0	20.0-29.0
Scaling		
Clear	0 (0%)	0 (0%)
Almost Clear	0 (0%)	0 (0%)
Mild	1 (5%)	0 (0%)
Moderate	15 (79%)	11 (65%)
Severe/Very Severe	3 (16%)	6 (35%)

Investigational product:
Drug name: Clobetasol propionate 0.05% spray
Active ingredient: Clobetasol propionate
Other ingredients: Isopropyl myristate, alcohol, undecylenic acid, sodium lauryl sulfate.
Batch Number: 859 (Item Number: 500199)

Results:
Each subject applied the study medication to all psoriatic plaques identified at Visit 1 twice daily for two or four weeks or until the investigator verified their psoriasis had cleared.

Subjects in the MITT 2-week treatment group had an average baseline percent BSA involvement of 20.84% to which they applied an average of 27.79 applications of study medication across an average of 13.89 days using 81.9 grams of study medication. The average percent BSA at the end of 2 weeks of treatment was 13.00%. Subjects in the 4-week treatment group had an average baseline percent BSA involvement of 20.71% to which they applied an average of 52.94 applications of study medication over an average of 26.53 days using 166.1 grams of study medication. The average percent of psoriatic involved BSA at the end of 2 weeks of treatment was 8.29%.

The wide variability in the Week 4 dosing parameters is related to the fact that two subjects (1 and 7) who were assigned to the 4-week treatment cleared by Week 2 and were consequently considered to have completed the study.

Serum cortisol level data after 2-week treatment are listed in Table 4.2.2.2.2. Based on 1 criterion (30-min post-stimulation level $\leq$ 18 µg/dL), at the end of the 2-week treatment period, 3 subjects out of 19 subjects (16%) showed signs of adrenal suppression (Subjects 13, 30, and 41). These three subjects showed normal serum cortisol levels within 16 days following the end of treatment. In addition, Subjects 1 and 7 who were randomized to 4-week treatment completed the study at Week 2 due to complete clearing. Their cosyntropin stimulation tests (CST) were performed at Week 2 (end of treatment). Subject 7 showed HPA axis suppression at Week 2 and was returned to normal 7 days following the end of treatment (Table 4.2.2.2.3). If including Subjects 1 and 7 to the 2-week treatment group, then 4 out of 21 subjects (19%) showed signs of adrenal suppression for the 2-week treatment.

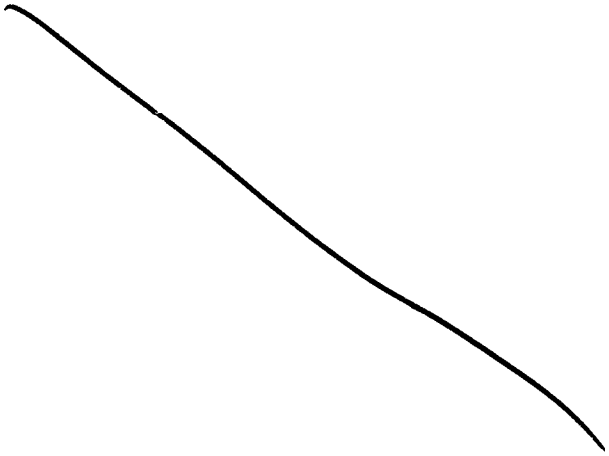
%BSA and HPA axis suppression status for each subject are listed in Table 4.2.2.2.4.

In the 2-week treatment group (N=19), the average pre-stimulation serum cortisol level at baseline was 14.87 µg/dL and at end of treatment was 9.94 µg/dL for a change of –4.93 µg/dL. The average post-stimulation serum cortisol level at baseline was 29.73 µg/dL and at end of treatment was 23.43 µg/dL for a change of –6.29 µg/dL.

Table 4.2.2.2.2. Cosyntropin Stimulation Test Results (2-Week Treatment).

2 Weeks Treatment

Subject	Visit 1 Pre	Visit 1 Post	Visit 3 Pre	Visit 3 Post	Follow-Up 1 Pre	Follow-Up 1 Post	Days Out from Visit 3	Follow-Up 2 Pre	Follow-Up 2 Post	Days Out from Visit 3



** The late follow-up was due to a misinterpretation of the post-stimulation cortisol data. The value of 18.0 µg/dL was not "flagged" as an abnormal response on the lab report and the subject was considered to have completed the study without adrenal suppression. This error was subsequently noted and the subject was contacted and completed a follow-up CST 16 days after the end of treatment.

‡ Subjects had baseline pre-cosyntropin samples drawn outside the 7-9am window specified in the protocol. Three of these subjects (31, 41 and 43) had samples taken 1 hour outside the specified window (Listing 6.1).

Δ Subjects had end of treatment pre-cosyntropin samples that were drawn outside the 7 to 9am window. (Listing 6.1).

∂ Subjects had end-of-treatment CST that was outside the +/- 1 hour window of the corresponding baseline test. The time beyond the specified time ranged from 80 to 94 minutes.

€ Subjects had pre-cosyntropin cortisol samples taken in the follow-up period that were outside the 7-9am window. The deviations were 17 and 20 minutes beyond the specified window (Listing 6.1).

† Subject had a follow-up CST that was fifteen minutes outside the +/- 1 hour timeframe of the baseline CST.

Ω Subject was seen 9 days after the first follow-up visit due to scheduling difficulties.

Serum cortisol level data after 4-week treatment are listed in Table 4.2.2.2.3. Based on 1 criterion (30-min post-stimulation level ≤ 18 µg/dL), at the end of the 4-week treatment period, 3 subjects out of 15 subjects (20%) showed signs of adrenal suppression (Subjects 4, 27, and 29). These three subjects had normal cortisol levels within 7 days following the end of treatment. As

mentioned earlier, Subjects 1 and 7 were excluded from HPA axis analysis for 4-week treatment because they only received the medication for 2 weeks due to complete clearing at Week 2.

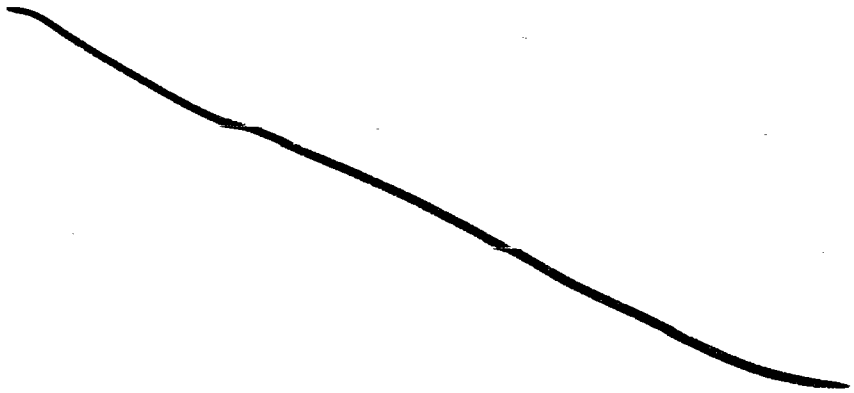
%BSA and HPA axis suppression status for each subject are listed in Table 4.2.2.2.4.

In the 4-week treatment group (N=17), average pre-stimulation serum cortisol level at baseline was 15.84 µg/dL and at end of treatment was 11.41 µg/dL for a change of –4.42 µg/dL. The average post-stimulation serum cortisol level at baseline was 29.62 µg/dL and at end of treatment was 24.75 µg/dL for a change of –4.86 µg/dL.

Table 4.2.2.2.3. Cosyntropin Stimulation Test Results (4-Week Treatment).

4 Weeks Treatment

	Visit 1		Visit 4		Follow-Up 1		Days Out	Follow-Up 2		Days Out
Subject	Pre	Post	Pre	Post	Pre	Post	from Visit 4	Pre	Post	from Visit 4



* Suppressed Subjects based on 3 criteria.

† Subject withdrew from the study after two weeks of follow-up because he did not want to have another CST performed.

‡ Subjects had baseline pre-cosyntropin samples drawn outside the 7-9am window specified in the protocol (Listing 6.1).

Δ Subject had end of treatment pre-cosyntropin samples that were drawn outside the 7 to 9am window. (Listing 6.1).

∂ Subjects had end-of-treatment CST that was outside the +/- 1 hour window of the corresponding baseline test. The time beyond the specified time ranged from 80 to 94 minutes.

€ Subject cleared after two weeks of treatment, discontinued therapy and had the CST performed

Table 4.2.2.2.4. % BSA and HPA axis suppression status for subjects in Study D02-0204-03.

2-Week Treatment			4-Week Treatment		
Subject No.	**%BSA at Baseline**	**HPA axis Suppression**	**Subject No.**	**%BSA at Baseline**	**HPA axis Suppression**
12	22	No	9	22	No
13	22	Yes	11	21	No
14	31	No	15	29	No
2	20	No	4	20	Yes
3	21	No	33	20	No
5	20	No	34	20	No
8	20	No	37	20	No
35	20	No	39	20	No
36	20	No	26	20	No
38	20	No	27	20	Yes
40	20	No	29	20	Yes
25	20	No	32	20	No
28	20	No	42	20	No
30	20	Yes	44	20	No
31	20	No	47	20	No
41	20	Yes			
43	20	No			
45	20	No			
46	20	No			
1[a]	22	No			
7[a]	20	Yes			

[a] Subjects 1 and 7 were randomized to 4 weeks treatment but completed the study at Week 2 due to complete clearing.

Discussion and Conclusions:

HPA axis suppression potential of clobetasol propionate spray, 0.05% was evaluated in adult patients with moderate to severe plaque psoriasis (≥ 20% BSA) by applying the medication twice daily for 2 or 4 weeks. The maximal usage condition was met as defined by the proposed labeling. In addition, a to-be-marketed formulation of the drug product was used. Under this condition, 4 out of 21 evaluable patients (19%) demonstrated HPA axis suppression at the end of 2-week treatment and 3 out of 15 evaluable patients (20%) demonstrated HPA axis suppression at the end of 4-week treatment. All these subjects' HPA axis function returned to normal after 7-16 days of discontinuation of therapy.

The data also suggest that HPA axis suppression is produced rapidly in susceptible individuals.

4.3 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-835	Brand Name	Clobex™
OCPB Division (I, II, III)	DPE III (HFD-880)	Generic Name	Clobetasol propionate
Medical Division	DDDDP (HFD-540)	Drug Class	Synthetic Fluorinated Corticorsteroids
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	Treatment of moderate to severe plaque psoriasis in patients 18 years and older
OCPB Team Leader	E. Dennis Bashaw, Ph.D.	Dosage Form	Spray, 0.05%
		Dosing Regimen	Twice-daily to the affected skin areas. Treatment should be restricted to 4 consecutive weeks and amounts less than 50 g/week.
Date of Submission	12/22/2004	Route of Administration	Topical
Estimated Due Date of OCPB Review	9/20/2005	Sponsor	Dow
PDUFA Due Date	10/27/2005	Priority Classification	New Dosage Form (3-S), 505 (b)(1)
Division Due Date			IND 62,543

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2	2	Systemic exposure to clobetasol propionate from application of Clobex (Clobetasol propionate) spary, 0.05% was evaluated in clinical investigations of hypothalamic-pituitary-adrenal axis function. Study TI01-01009* Study D02-0204-03* * 3 criteria were used for HPA axis suppression
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Vasoconstrictor studies to determine potency	**X**	**1**	**1**	**Study TI00-01003**
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**3**	**3**	

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?		•
QBR questions (key issues to be considered)	• **Use the to-be-marketed formulation?** • **Were the HPA axis results obtained under maximal usage conditions?** • **Do the HPA axis results support safe use of this product?**	
Other comments or information not included above	**This is an eCTD submission.**	
Primary reviewer Signature and Date	**Lei Zhang, 3/14/2005 (Filing)** **Lei Zhang, 9/26/2005 (Review)**	
Secondary reviewer Signature and Date	**Raman Baweja, 3/14/2005 (Filing)** **Dennis Bashaw, 9/26/2005 (Review)**	

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

/s/

Lei Zhang
9/28/2005 12:46:17 PM
BIOPHARMACEUTICS

Dennis Bashaw
9/28/2005 03:29:31 PM
BIOPHARMACEUTICS

John Lazor
9/30/2005 06:40:14 PM
BIOPHARMACEUTICS