CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA: 22-013

Letter Date: 3/14/06

Proposed Brand Name: Primolux®

Generic Name: Clobetasol Propionate

Reviewer(s): Suliman I. Al-Fayoumi, Ph.D.

Team Leader: Abimobola Adebowale, Ph.D.

OND Division: Dermatology and Dental Products

OCPB Division: Division of Clinical Pharmacology 3

Sponsor: Connetics

Submission Type: Original NDA

Formulation, Strength(s): Foam formulation, 0.05%

Proposed Indications & Dosage Regimens: Topical Treatment of Inflammatory and Pruritic Manifestations of Corticosteroid-Responsive Dermatoses, to be applied twice daily for up to two weeks not to exceed 50 g per week

1. Executive Summary

Clobetasol propionate is a synthetic corticosteroid that has been marketed in the US since 1985 for the treatment of corticosteroid-responsive dermatoses. Due to their anti-inflammatory actions, topical corticosteroids, including clobetasol propionate, are the mainstay for treatment of corticosteroid-responsive dermatoses of the skin and scalp. Topical corticosteroids often are effective rapidly and then can be used intermittently to decrease their potential to cause skin atrophy, growth retardation, adrenal suppression, or osteopenia.

Clobetasol propionate is currently marketed in the US at a 0.05% strength in multiple dosage forms including, lotion, cream, ointment, gel, solution, shampoo, emollient cream, foam and spray.

Clobetasol propionate foam, 0.05% (EF Clobetasol foam) is formulated in an ethanol-free, petrolatum-based emulsion foam. The sponsor anticipates better patient compliance with the foam formulation because of the localized application and improved pharmaceutical properties relative to other currently marketed dosage forms such as the cream and ointment.

The current application is submitted under the 505(b)(2) provision utilizing Temovate® (clobetasol propionate) ointment, 0.05% as the Reference Listed Drug (RLD).

The clinical program in support of the application consists of 7 clinical studies in 1274 subjects, including two Phase 3 safety and efficacy trials in patients with atopic dermatitis

and psoriasis, a vasoconstriction (skin blanching) study, a dermal irritation study, a dermal sensitization study, an HPA axis suppression study and a comparative relative bioavailability study.

Overall, the clinical pharmacology findings indicate that application of clobetasol propionate ointment results in greater systemic exposure than EF clobetasol propionate foam, as evidenced by higher mean Cmax and $AUC_{(0-12)}$ values following multiple dose application relative to EF clobetasol propionate foam. The relative bioavailability of EF clobetasol propionate foam is 35.7% when compared to clobetasol propionate ointment.

1.1 Recommendation

From a clinical pharmacology perspective, the clinical pharmacology data submitted under NDA 22-013 support the reliance on the Agency's findings of systemic safety for Temovate® (clobetasol propionate) ointment, 0.05% for the approval of EF Clobetasol foam, 0.05% in patients with corticosteroid-responsive dermatoses. From the view point of the Office of Clinical Pharmacology, NDA 22-013 is **Acceptable**. See Appendix 4.1 for sponsor and Agency proposed labeling recommendations. Additional labeling comments may be forthcoming pending further discussion with the Medical Review Team.

1.2 Phase 4 Commitments

None.

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1.3 Summary of CPB Findings

Data was submitted from 7 clinical studies in support of the application, including two Phase 3 safety and efficacy trials in patients with atopic dermatitis and psoriasis, a vasoconstriction (skin blanching) study, a dermal irritation study, a dermal sensitization study, an HPA axis suppression study and a comparative relative bioavailability study.

The current review evaluated the adequacy of three clinical pharmacology-related studies to support the application, namely studies CPE.C.101 (vasoconstriction study), CPE.C.201 (HPA axis suppression study) and CPE.C.202 (comparative relative bioavailability study).

Study CPE.C.101 was a single-center, randomized, blinded comparison of the vasoconstrictor potency of 10 mg single doses of EF Clobetasol foam, 0.05%, clobetasol emollient cream, 0.05%, and fluticasone propionate ointment, 0.005% in healthy adult male and female subjects (n = 36; 30F & 6M, mean age 42 yrs).

The results of study CPE.C.101 indicate that clobetasol Emollient Cream showed the greatest degree of vasoconstriction, followed by Fluticasone ointment and then EF Clobetasol foam (see Table 1). The EF clobetasol Foam formulation demonstrated a statistically significant difference on vasoconstrictor score relative to placebo.

Study CPE.C.201 was a multi-center, open-label study in male and female adult and pediatric patients (n = 52; 22M & 30F) with atopic dermatitis, to evaluate the effect of EF clobetasol foam on the HPA axis, following twice daily application to a minimum of 30% treatable BSA for two weeks (up to 50 g per week).

The results of study CPE.C.201 indicate that the proportion of patients demonstrating HPA axis suppression was 24% (5/21) of patients in cohort 1 ($\geq$ 18 yrs), 0% (0/15) of patients in cohort 2 ($\geq$ 12 yrs < 18 yrs), and 47% of patients in cohort 3 ($\geq$ 6 yrs < 12 yrs). However, the flawed study design casts doubt into the validity of the study findings.

Study CPE.C.202 was a randomized, open-label, parallel-design study to assess the relative bioavailability of EF clobetasol propionate foam, 0.05% and clobetasol propionate ointment, 0.05% following twice daily applications of 3.5 g doses for 2 weeks in patients with mild to moderate Plaque-Type Psoriasis (n = 32; 19M & 13F, age 24-72 yrs).

The results of study CPE.C.202 indicate that application of clobetasol propionate ointment results in greater systemic exposure than EF clobetasol propionate foam, as evidenced by higher mean Cmax and $AUC_{(0\text{-}12)}$ values relative to EF clobetasol propionate foam. The relative bioavailability of EF clobetasol propionate foam is 35.7% when compared to clobetasol propionate ointment.

Overall, the flawed design of the HPA axis suppression study (i.e., CPE.C.201) did not allow for conclusive safety findings related to the potential for HPA axis suppression with EF clobetasol propionate foam. Moreover, study CPE.C.202, a robust comparative relative bioavailability study, demonstrated lower systemic exposure with EF clobetasol propionate foam, 0.05% relative to clobetasol propionate ointment, 0.05%. However, the relationship between the systemic exposure and the potential for HPA axis suppression is unknown.

2 Question-Based Review

2.1 General Attributes

Clobetasol propionate is a potent synthetic corticosteroid, with a high degree of glucocorticoid activity and minimal mineralocorticoid activity. Hence, it possesses anti-inflammatory, antipruritic and vasoconstrictive properties.

The sponsor seeks approval of clobetasol propionate foam formulation, 0.05% for the treatment of corticosteroid-responsive dermatoses. In support of the application, the sponsor intends to rely on the Agency's findings of safety for Temovate® (clobetasol propionate) ointment, the designated Reference Listed Drug (RLD).

2.2 General Clinical Pharmacology

1. Has the pharmacological activity of clobetasol propionate foam formulation, 0.05% been adequately characterized?

Clobetasol propionate is a synthetic analog of prednisolone. It has been marketed in the US since 1985 in a variety of dosage forms for the treatment of corticosteroid-responsive dermatoses.

Topical corticosteroids are known to produce blanching or vasoconstriction in the microvasculature of the skin. This property is regarded as a surrogate of the potency of the topical corticosteroid. In addition, the systemic bioavailability of corticosteroids as evidenced by the extent of HPA axis suppression has traditionally been relied upon as a surrogate of the systemic safety of the topical corticosteroid.

Vasoconstriction Study

The sponsor conducted study CPE.C.101 to evaluate the vasoconstriction activity of EF Clobetasol foam, 0.05%. The study was intended to bracket the anticipated relative potency of EF Clobetasol foam by selecting a corticosteroid of similar potency (i.e., clobetasol emollient cream, 0.05%) and one of lower potency (i.e., fluticasone propionate ointment, 0.005%) as comparators. This study was based on the dose-duration response study design as presented in the FDA Guidance for Industry entitled: *Topical Dermatological Corticosteroids: In vivo Bioequivalence* (June, 1995).

Study CPE.C.101 was a single-center, randomized, blinded comparison of the vasoconstrictor potency of 10 mg single doses of EF Clobetasol foam, 0.05%, clobetasol emollient cream, 0.05%, and fluticasone propionate ointment, 0.005% in healthy adult male and female subjects (n = 36; 30F & 6M, mean age 42 yrs).

All subjects enrolled in this study were healthy male and female subjects between the ages of 18 and 65 years who demonstrated a vasoconstrictor response to a 10 mg application of fluticasone propionate ointment, 0.005% to a small area on the upper arm with a visual evaluation the following day, or had a previously documented history of vasoconstrictive response to topical corticosteroids.

In the study, subjects had three test sites demarcated on each ventral forearm. Two sites remained untreated and acted as control sites. Four test sites were treated with the test products. The test products and untreated control sites were randomly assigned following a randomization scheme available only to the individual applying the test products. Test products remained on the skin under a non-occlusive guard for a dose-duration period of 16 hours. Product application in a given subject was considered to be 'simultaneous' that is, all test products were administered in a 2 to 3 minute time period. The skin blanching score was visually assessed for all sites approximately 18 hours (± 1 hour) after study drug application using the Scale for Visual Assessment of Skin Blanching.

Clobetasol Emollient Cream showed the greatest degree of vasoconstriction, followed by fluticasone ointment and then EF Clobetasol foam (Table 1). The EF clobetasol foam formulation demonstrated a statistically significant difference on vasoconstrictor score relative to placebo. While EF clobetasol foam showed a statistically significant difference relative to clobetasol emollient cream, no statistically significant difference was shown between EF clobetasol foam and fluticasone ointment.

Table 1. Mean Vasoconstrictor Scores in study CPE.C.101

Mean Vasoconstrictor Score	Test Articles
0.1389	Vehicle Foam
1.444	EF Clobetasol Foam
1.7500	Fluticasone Ointment
2.0278	Clobetasol Emollient Cream

Reviewer Comments:

The sponsor's contention that EF clobetasol foam, 0.05% is a [redacted] is not supported by the findings of study CPE.C.101. Therefore, statements to that effect have been deleted from the proposed package insert.

HPA Axis Suppression Study

Study CPE.C.201 was a multi-center, open-label study in male and female adult and pediatric patients (n = 52; 22M & 30F) with atopic dermatitis, to evaluate the effect of EF clobetasol foam on the HPA axis, following twice daily application to a minimum of 30% treatable BSA for two weeks (up to 50 g per week).

The study design entailed sequential enrollment of patients based on age so that younger patients are administered the drug only following completion of older patient cohorts. The original study design included the following cohorts:

- Cohort 1: ≥ 18 yrs
- Cohort 2: ≥ 12 yrs < 18 yrs
- Cohort 3: ≥ 6 yrs < 12 yrs
- Cohort 4: ≥ 3 yrs < 6 yrs

- Cohort 5: ≥ 3 months < 3 yrs

The effect on HPA axis was determined by response to cosyntropin stimulation tests at screening, Week 2 and at a conditional visit if suppression was demonstrated at the Week 2 visit (a normal response is a post-injection serum cortisol level > 18 µg/dL).
A cosyntropin stimulation test involved drawing a blood sample from subjects immediately before, and 30 min after I.V. or I.M. injection of cosyntropin. These blood samples were ~~to~~ then analyzed for serum cortisol levels.

No patients were enrolled into cohorts 4 and 5 since patients in cohort 3 demonstrated marked HPA axis suppression.

Overall, the study results (Table 2) indicated that the proportion of patients demonstrating HPA axis suppression was 24% (5/21) of patients in cohort 1 (≥ 18 yrs), 0% (0/15) of patients in cohort 2 (≥ 12 yrs < 18 yrs), and 47% of patients in cohort 3 (≥ 6 yrs < 12 yrs).

All subjects who demonstrated HPA axis suppression at Week 2 had serum cortisol levels > 18 µg/dL at the conditional visit and were considered to have reversed their HPA axis suppression.

Table 2. Incidence of HPA axis suppression by patient cohort

	Cohort 1	Cohort 2	Cohort 3	Total
Number of Subject	22	15	15	52
Week 2/End of Treatment				
n	21	15	15	51
Suppression	5 (24%)	0 (0%)	7 (47%)	12 (24%)
Conditional Visit				
n	5	0	7	12
Reversible Suppression	5 (100%)	NA	7 (100%)	12 (100%)

Reviewer Comments:

The sponsor was specifically advised by FDA at a Regulatory Guidance meeting held on Nov 23, 2003 that administration of cosyntropin to the same subject repeatedly at intervals less than four weeks may result in higher stimulated cortisol levels after each successive cosyntropin injection, leading to invalid data. Evaluation of HPA axis function should be performed at baseline and at the end of treatment at a minimum. For studies longer than 4 weeks, cosyntropin testing should be performed no more frequently than every four weeks.

In the current study, cosyntropin was administered to patients over an interval of only 2 weeks. Moreover, three patients in cohort 1 who demonstrated HPA axis suppression were reported to have applied > 150 g of the study drug in the 2-week treatment period. Consequently, the flawed study design casts doubt into the validity of the study findings. As such, no valid conclusions may be drawn from the study.

Safety and Efficacy Summary

Two Phase 3 efficacy and safety trials were submitted under the current application for the indication of corticosteroid responsive dermatoses. The first Phase 3 study was in subjects with moderate to severe atopic dermatitis (CPE.C.301) and evaluated the superiority of EF Clobetasol to Emulsion Formulation Clobetasol Propionate Vehicle foam. Study CPE.C.301 included 101 patients 12-18 yrs of age with moderate to severe atopic dermatitis. In the study, a total of 377 subjects were randomized to one of two parallel treatment groups in a 2:1 ratio (EF Clobetasol foam:Vehicle foam). The primary endpoint of the study was the proportion of subjects who achieved treatment success defined as an investigator Static Global Assessment (ISGA) score of 0 or 1, a score of 0 or 1 for erythema and induration/papulation at Week 2, and a minimum improvement in the ISGA score of two grades from Baseline to Week 2.

The second Phase 3 study was in subjects with mild to moderate psoriasis (CPE.C.302) and also evaluated the superiority of EF Clobetasol to its Vehicle foam. Additionally, a third arm was added to the psoriasis study to establish a clinical bridge so that the short-term and long-term safety data of the RLD, Temovate ointment, may be referenced. A total of 497 subjects were randomized to one of three parallel treatment groups in a 2:1:1 ratio (EF Clobetasol foam:Temovate ointment:Vehicle foam). Study CPE.C.302 included 9 patients 12-18 yrs of age with moderate to severe atopic dermatitis. The primary endpoint of the study was identical to that utilized in the study CPE.C.301.

In conclusion, EF Clobetasol foam, 0.05% demonstrated superiority to Vehicle foam for the primary endpoint in the studies CPE.C.301 ($p < 0.0001$) and CPE.C.302 ($p = 0.0005$). Moreover, for all of the secondary endpoints of both studies, EF Clobetasol foam was highly statistically superior to Vehicle foam (Tables 3 & 4).

Table 3. Patients with treatment success at Week 2 in study CPE.C.301 (ITT population)

	EF Clobetasol Foam	Vehicle Foam
Number of subjects	251	126
Success	131 (52%)	18 (14%)
P-value[a]		< 0.0001

Table 4. Patient with treatment success at Week 2 in study CPE.C.302 (ITT population)

	EF Clobetasol Foam	Vehicle Foam
Number of Subjects	253	123
Success	41 (16%)	5 (4%)
P-value[a]		0.0005

The safety of EF Clobetasol foam was evaluated in four studies in subjects with atopic dermatitis (CPE.C.201 and CPE.C.301) or psoriasis (CPE.C.202 and CPE.C.302) receiving twice daily treatment for 2 weeks. In addition, the sponsor sought to rely on the

Agency's findings of systemic safety for clobetasol propionate ointment, 0.05%, based on the findings of a bridging relative bioavailability study (study CPE.C.202).

The most common adverse event reported with EF Clobetasol foam was application site reaction which was reported in 2% of the subjects in the assessed safety population.

2.3 General Biopharmaceutics

1. What is the composition of the formulation?

Emulsion Formulation Clobetasol Propionate foam, 0.05% (EF Clobetasol foam) is a petrolatum-based emulsion aerosol foam (see Table 5 for detailed composition of the formulation). EF Clobetasol foam is packaged in an aluminum container lined internally with a [redacted] that is fitted with an [redacted] valve, an actuator, and a non-product contacting cap. It is supplied in a 100 g dose strength.

Table 5. Composition of the proposed EF clobetasol foam formulation

Component	Reference to Quality Standard	Function	%w/w[1]
Clobetasol propionate	USP	Active ingredient	0.05
Propylene Glycol	USP	[redacted]	[redacted]
Phenoxyethanol	NF		
White Petrolatum	USP		
Light Mineral Oil	NF		
Isopropyl Myristate	NF		
Sorbitan Monolaurate	NF		
Cetyl Alcohol	NF		
Cyclomethicone	NF		
Purified Water	USP		
Anhydrous Citric Acid	USP		
Potassium Citrate (Monohydrate)	USP		
Polyoxyl 20 Cetostearyl Ether	NF		

[1] Per can concentrations

2. Has an adequate link been demonstrated between EF Clobetasol propionate foam, 0.05% and the RLD (i.e., clobetasol propionate ointment, 0.05%)?

The sponsor conducted a relative bioavailability study comparing EF clobetasol propionate foam, 0.05% to clobetasol propionate ointment, 0.05%, the selected RLD. The comparative relative bioavailability study was intended to allow reliance on the Agency's

findings of safety for clobetasol propionate ointment, 0.05% in support of the safety of EF clobetasol propionate foam, 0.05%.

Study CPE.C.202 was a randomized, open-label, parallel-design study to assess the relative bioavailability of EF clobetasol propionate foam, 0.05% and clobetasol propionate ointment, 0.05% following twice daily applications of 3.5 g doses for 2 weeks in patients with mild to moderate Plaque-Type Psoriasis (n = 32; 19M & 13F, age 24-72 yrs).

Blood samples were collected for determination of clobetasol propionate plasma concentrations at -1, 1, 3, 6 and 12 hrs after the first application on treatment day 8. Additional blood samples were collected at -1 and 1 hr after the first application on treatment day 15. The following PK parameters were calculated on day 8 for each treatment: Cmax, tmax and $AUC_{(0-12)}$.

Overall, the study findings indicate that application of clobetasol propionate ointment resulted in greater systemic exposure than EF clobetasol propionate foam, as evidenced by higher mean Cmax and $AUC_{(0-12)}$ values relative to EF clobetasol propionate foam (Fig. 1). The relative bioavailability of EF clobetasol propionate foam is 35.7% when compared to clobetasol propionate ointment (Table 6).

Table 6. Mean PK parameters of clobetasol propionate on day 8

	Cmax (pg/mL)	Tmax (h)	$AUC_{(0-12)}$ (pg·h/mL)
EF Clobetasol Foam			
N	15	14	15
Mean (SD)	59.0(36.2)	4.7(4.4)	562.0(336.0)
Median (min, max)	48.0(0.0, 132.3)	3.0(0.0, 12.0)	481.6(0.0, 1209.4)
%CV	61.4	92.0	59.8
Temovate Ointment			
N	16	15	16
Mean (SD)	188.1(274.2)	5.3(3.7)	1572.9(2436.8)
Median (min, max)	100.5(0.0, 1104.3)	6.0(1.0, 12.0)	796.4(0.0, 10133.1)
%CV	145.8	69.8	154.9

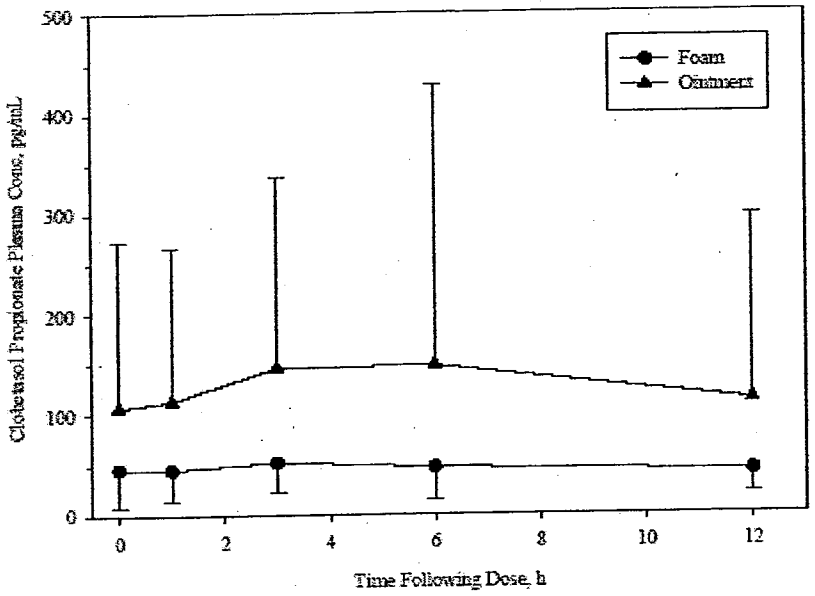

Fig. 1. Mean plasma concentrations of clobetasol propionate on day 8

Reviewer Comments:

At a Special Protocol Assessment meeting held with the sponsor on March 2, 2005, the Division stated that "establishment of a clinical bridge to the Reference Listed Drug (Temovate ointment) would rest on demonstration that the sponsor's product was not superior to the RLD for efficacy (in a three-arm psoriasis trial), did not have a worse safety profile than the RLD, and did not demonstrate greater systemic bioavailability as demonstrated in a comparative HPA axis suppression study or a very robust PK study".

2.4 Analytical Section

1. Have the analytical methods been adequately validated?

A validated LC/MS/MS analytical assay method was developed and used to quantify clobetasol propionate in the comparative relative bioavailability study (CPE.C.202)

A validated method was developed for the determination of clobetasol propionate concentrations in human plasma using high-performance liquid chromatography (HPLC) with mass spectrometric (MS/MS) detection.

Details of the analytical assay method validation are as follows:

- Working concentration range: [redacted] ng/mL.

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X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

3 Detailed Labeling Recommendations

The key clinical pharmacology labeling recommendations are summarized as follows:

- Under **Pharmacokinetics** subsection of the **CLINICAL PHARMACOLOGY** section, the following statement was inserted:

"Following twice daily application of [redacted] for one week to 32 adult patients with mild to moderate plaque-type psoriasis, mean peak plasma concentrations of clobetasol were observed around 5 hours post-dose on day 8."

- Under **Pharmacokinetics** subsection of the **CLINICAL PHARMACOLOGY** section, the following statement was deleted:

[redacted]

- Under **INDICATIONS AND USAGE** section, the following statement was revised as follows:

"Primolux Foam is [redacted] indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses."

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4 Appendix

4.1 Proposed labeling (original and Agency proposed)

4.2 OCP Filing and Review Form

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Appendix 4.1

Proposed Package Insert

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_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Appendix 4.2

Cover Sheet and OCP Filing/Review Form

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-013	Proposed Brand Name	Primolux
OCP Division	DCP 3	Generic Name	Clobetasol Propionate
Medical Division	Dermatology & Dental Products	Drug Class	Corticosteroid
OCP Reviewer	Suliman Al-Fayoumi	Indication(s)	Treatment of corticosteroid-responsive Dermatoses
OCP Team Leader	Abimbola Adebowale	Dosage Form	Foam, 0.05%
		Dosing Regimen	BID
Date of Submission	3/14/06	Route of Administration	Topical
Estimated Due Date of OCP Review	9/30/06	Sponsor	Connetics
PDUFA Due Date	11/14/06	Priority Classification	Standard
Estimated Division Due Date	10/14/06		

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			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
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:				
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:	X	2	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:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	3	3	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)	**Has an adequate link been demonstrated between EF Clobetasol propionate foam, 0.05% and the RLD (i.e., clobetasol propionate ointment, 0.05%)?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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/s/

Suliman Alfayoumi
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