CLINICAL PHARMACOLOGY REVIEW

NDA #:	210566/S-003
Submission Date:	02/24/2020 (SDN 62)
Brand Name:	LEXETTE®
Generic Name:	Halobetasol propionate foam, 0.05%
Dosage Form:	Topical
Dosage Strength:	0.05%
Reviewer:	Luke Oh, Ph.D.
Team Leader:	Chinmay Shukla, Ph.D.
OCP Division:	Division of Inflammation and Immune Pharmacology
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Mayne Pharma LLC
Submission Type:	Efficacy supplement
Indication Sought:	Plaque psoriasis in patients 12 years of age and older

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1. EXECUTIVE SUMMARY

LEXETTE® foam contains 0.05% Halobetasol propionate (HBP) is as an active ingredient, which is a potent corticosteroid, which has been used to treat dermal diseases for over several years. This product was approved in 2018 for the treatment of plaque psoriasis in adults.

At the time of approval, maximal use pharmacokinetic (PK) and hypothalamic-pituitary-adrenal (HPA) axis suppression study in adolescent subjects between the ages of 12 years to less than 17 years was requested as a post marketing requirement (PMR). For the same study, the Agency issued a written request on November 29, 2017 and a revised written request was issued on June 01, 2018. The language of the PMR in the approval letter is shown below.

3344-1 Conduct a maximal use pharmacokinetic (PK) and HPA axis suppression study in subjects 12 years to < 17 years of age with psoriasis.

This supplement contains a study report for the maximal use PK and HPA axis suppression in adolescent subjects.

1.1 Recommendation

From a Clinical Pharmacology perspective, this supplement is acceptable provided the labeling comments are adequately addressed by the Applicant. Clinical Pharmacology further recommends that the applicant has fulfilled PMR 3344-1 and has fulfilled the revised written request that was issued on June 01, 2018.

1.2 Post marketing requirement (PMC) or Post marketing commitment (PMC)

None.

2. DETAILED REVIEW OF THE STUDY REPORT

Protocol Number: 122-0551-209

Study title: An Open Label Evaluation of the Adrenal Suppression Potential and Pharmacokinetic (PK) Properties of Twice Daily Halobetasol Propionate (HBP) Foam, 0.05% in Subjects 12 to Less Than 18 Years of Age with Plaque Psoriasis Receiving Two Weeks of Treatment.

Primary objective: The objective of this study was to determine the adrenal suppression potential and the PK properties of HBP Foam, 0.05% applied twice daily in male and female subjects who were 12 to less than 18 years of age with stable plaque psoriasis.

Summary of the study design: This was an open label, multicenter PK study of HBP Foam, 0.05% in male and female subjects 12 years to less than 18 years with at least moderate plaque psoriasis (IGA Score of at least 3). Twenty four subjects with at least 10% BSA involvement (excluding the face, scalp, groin, axillae and other intertriginous areas) were enrolled in this study in the US and Europe. All subjects completed the safety evaluation of the study; however, only 23 subjects completed the PK portion of the study. One subject (21-002) was excluded from the PK population due to use of a prohibited medication (i.e. Squamax emulsion which contains urea and salicylic acid).

Since this was only a 2 week treatment, for the assessment of HPA axis suppression, all subjects had their pre-treatment cosyntropin stimulation test (CST) conducted at least 20 days before the baseline visit so that there is at least a 4 week interval between pre and post stimulation CST. At the baseline visit, only subjects with normal adrenal function were eligible to participate in this study. Subjects were instructed to apply HBP Form twice a day (approximately every 12 hours) to all psoriasis plaques identified at baseline. The maximum dose was specified as approximately 50 grams per week. All subjects had CST at the end of the treatment to assess HPA axis suppression. Abnormal HPA axis was defined as post-CST serum cortisol level of $\leq$ 18 µg/dL. PK blood samples were drawn at baseline, pre-dose on Day 8 and post-treatment on Day 15 at 12 hours ± 30 minutes post evening dose on previous day (Day 14).

Demographic information: Summary of demographics is shown in Table 1 below.

Table 1: Summary of demographics in the PK population

CHARACTERISTIC	HBP Foam, 0.05% N=23
SEX, n (%)	
Female	10 (43.5)
Male	13 (56.5)
AGE (years)	
Mean	14.8
Standard Deviation	1.79
Median	14.8
Minimum, Maximum	12.1, 17.7
ETHNICITY, n (%)	
Hispanic or Latino	6 (26.1)
Not Hispanic or Latino	17 (73.9)
RACE, n (%)	
White	23 (100.0)

Source: Sponsor's study report Table 11.2.1-2

Reviewer comments: *It is noted that all subjects in this study were white. Although an adequate representation of race is highly desirable; there has not been any concreate evidence to suggest any effect of race based on the limited past PK experience. Furthermore, plaque psoriasis disease manifestation does not appear to exhibit any*

racial variability. Hence the lack of ethnic diversity is unlikely to impact the regulatory outcome.

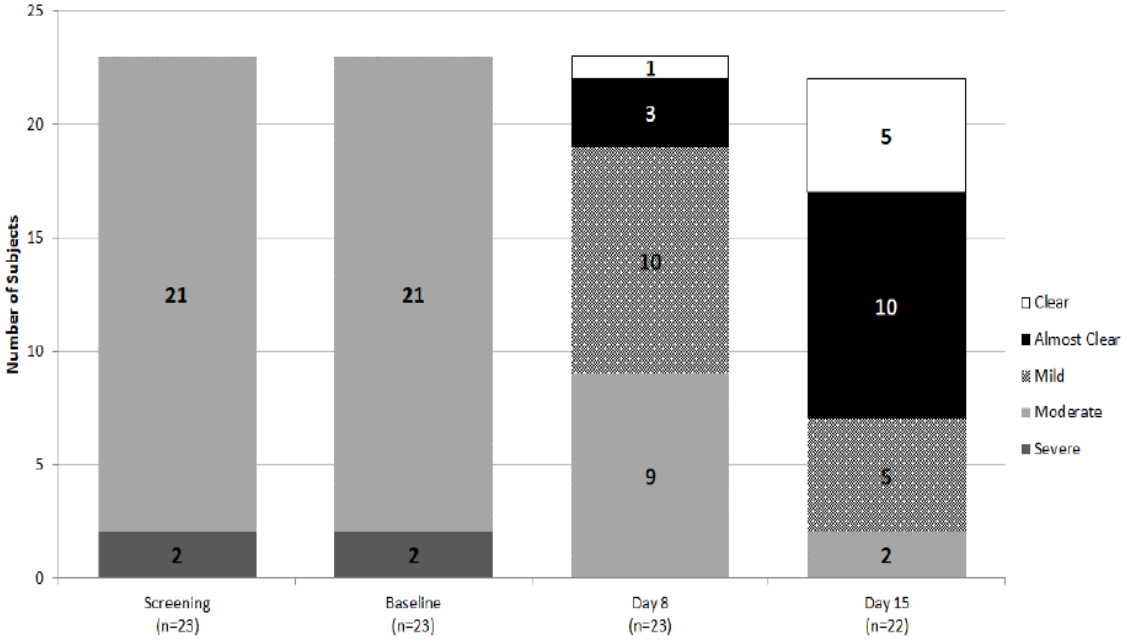
Within the lowest age range, i.e. between 12 years to 14 years, there were 12 subjects and this is acceptable.

Baseline disease severity: At Baseline the mean percent body surface area (BSA) affected with disease was 15.1% with a range of 11% to 23%. By Day 8, the mean percent BSA affected with disease decreased to 12.7% with a range of 0% to 23%. At Day 8, the mean change from Baseline was -2.4 with a range of -15 to 1. By Day 15, the mean percent BSA affected with disease decreased to 9.1% with a range of 0% to 23%. At Day 15, the mean change from Baseline was -6.2 with a range of -22 to 0.

Reviewer comments: *To be under maximal use conditions, BSA involvement of at least 10% is recommended in adolescent subjects and this study is acceptable in terms of BSA involvement at baseline.*

Figure 1 below provides a pictorial representation of disease severity (IGA) and resolution of disease at each study visit.

Figure 1: Disease severity at baseline and at each study visit

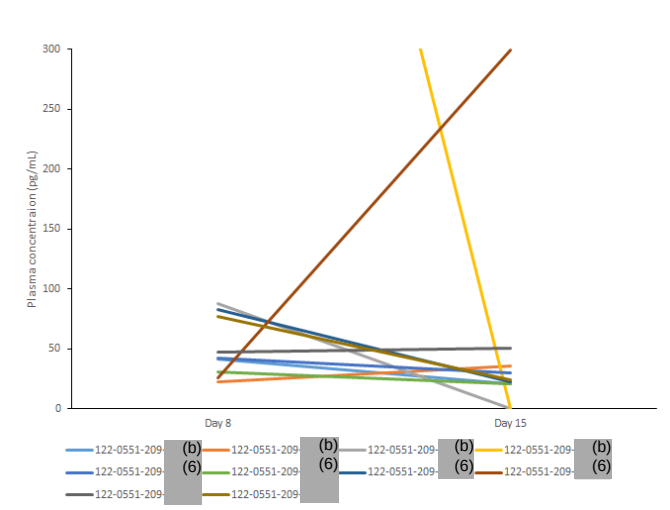


Source: Sponsor's study report Figure 11.4.1.1-1

Reviewer comments: *For a maximal use study, subjects at the upper range of disease severity are recommended to be enrolled. Since all subjects enrolled were of at least moderate severity at baseline, this study is acceptable. Additional analysis evaluating a potential impact of disease (i.e., IGA score change from Day 8 to Day 15) on PK level was conducted by the reviewer.*

Reviewer analysis: *There were 10 subjects with measurable PK levels on Days 8 and 15. One subject ((b) (6)) had notably high plasma HBP level (975 pg/mL) on Day 8, and the level became below quantitative level (BQL) on Day 15. Subject (b) (6) had plasma HBP level of 25.9 pg/mL on Day 8, but the level increased to 299 pg/mL on Day 15. There were 7 out of 10 subjects who have plasma PK level decreased by Day 15. There were 5 out of 10 subjects who had lower IGA score on Day 15 than Day 8, and of these 5 subjects, three subjects showed a decrease of plasma HBP levels on Day 15. The number of subjects appears too small to draw any conclusion regarding the impact of efficacy on the PK level of HBP in this study.*

Figure 2. Comparison of plasma HBP level of each subjects on Days 8 and 15 (Reviewer's analysis)



Percent body surface area threated through the treatment duration: At baseline in the evaluable population, the mean % BSA treated was 14.5% with a range of 10% to 20%. By Day 8, the mean % BSA treated decreased to 12.6% with a range of 5% to 20%. By Day 8, the mean change from baseline was -1.9 with a range of -15 to 1.

Treatment compliance: A subject was considered compliant with the dosing regimen if the subject applied at least 80% but no more than 120% of the expected number of applications according to the data reported in the subject's diary. All canisters of test article were weighed when dispensed and when they were returned. Summary of treatment compliance is shown in Table 2.

Table 2: Treatment compliance

Parameter	HBP Foam (N=23)
Compliant[1], n (%)	
Yes	23 (100.0)
No	0 (0.0)
Number of Days Dosed (days)	
N	23
Mean	14.1
S.D.	1.52
Median	14.0
Min., Max.	9, 17
Total Number of Applications	
N	23
Mean	28.3
S.D.	3.03
Median	28.0
Min., Max.	18, 34
Percent of Expected Doses Applied	
N	23
Mean	100.6
S.D.	4.23
Median	100.0
Min., Max.	92.9, 107.1

Source: *Sponsor's study report Table 14.2.1.2*

The average total amount of formulation (i.e. dose) used was 85.3 grams in the PK population with a range of 20.1 grams to 124.4 grams. The daily average dose was 6.1 grams with a range of 1.3 grams to 8.6 grams. The average amount of dose used was 1.4 mg/cm^2 with a range of 0.5 mg/cm^2 to 2 mg/cm^2 in all populations.

There were 6 subjects (Subjects [redacted] (b) (6)) in with an abnormal HPA response (a post-stimulation serum cortisol level of ≤ 18µg/dL). The average total dose used was 85.6 grams (range: 20.1 grams to 124.4 grams) for suppressed subjects and 85.1 grams (range: 36.6 grams to 108.6 grams) for non-suppressed subjects. The daily average dose was 6.0 grams (range: 1.3 grams to 8.2 grams) for suppressed subjects and 6.1 grams (range: 2.4 grams to 8.6 grams) for non-suppressed subjects. The average dose used was 1.4 mg/cm^2 and 1.3 mg/cm^2 for suppressed and non-suppressed subjects, respectively, with a range of 0.5 mg/cm^2 to 2 mg/cm^2 for both groups.

Hence there does not seem to be any relationship between dose and HPA axis suppression and the summary of dosing in subjects that were suppressed versus subjects that were not suppressed is shown in Table 3.

Table 3: Summary of dosing

Parameter	HBP Foam (N=23)	Suppressed (N=6)	Non-Suppressed (N=17)
Total amount of drug used (g)			
N	23	6	17
Mean	85.3	85.6	85.2
S.D.	24.44	37.13	19.77
Median	94.1	89.6	94.1
Min., Max.	20.1, 124.4	20.1, 124.4	36.6, 108.6
Daily average test article used (g)			
N	23	6	17
Mean	6.1	6.0	6.1
S.D.	1.76	2.47	1.54
Median	6.5	6.7	6.5
Min., Max.	1.3, 8.6	1.3, 8.2	2.4, 8.6
Amount of test article used (mg/cm^2)			
N	23	6	17
Mean	1.4	1.4	1.3
S.D.	0.47	0.59	0.44
Median	1.4	1.7	1.3
Min., Max.	0.5, 2	0.5, 2	0.5, 2

Source: Sponsor's submission Table 14.3.1.2

Trough concentrations of halobetasol propionate: Blood for PK analysis was drawn 3 times: at screening, pre-dose on Day 8 and on Day 15 at 12 hours post evening dose on previous day (i.e. Day 14).

At Screening, all morning trough concentration of halobetasol propionate in plasma were below the quantifiable limit (BQL <20.0 pg/mL).

On Day 8, 14 of the 23 subjects the morning trough plasma concentrations of HBP were BQL. In the remaining 9 subjects the average plasma HBP concentration was 154.6 pg/mL with a range of 23 pg/mL to 975 pg/mL.

On Day 15 (end of study), 13 of the 23 subjects the morning trough plasma concentrations of HBP were BQL (For subject (b) (6), PK blood sample is missing as blood was drawn less than 12 hours from the previous dose). In the remaining 9 subjects the average plasma concentration was 59.9 pg/mL with a range of 21 pg/mL to 299 pg/mL. Summary of systemic concentrations on Day 8 and Day 15 is shown in Table 4.

Table 4: Summary of quantifiable systemic concentrations on Day 8 and Day 15

Visit	Statistic	HBP Foam (N=23)
Screening	n	0
Day 8	n	9
	Mean	154.6
	S.D.	308.67
	Median	47.1
	Min., Max.	23, 975
	Geometric Mean	64.6
	Coefficient of Variation	199.7
Visit 4/Day 15/EOS	n	9
	Mean	59.9
	S.D.	90.15
	Median	29.7
	Min., Max.	21, 299
	Geometric Mean	37.3
	Coefficient of Variation	150.5

Source: Sponsor's submission Table 14.2.7

Table 5 shows the 9 subjects with measurable HBP plasma concentrations. Six subjects (26.1%) showed evidence of HPA axis suppression out of which only 3 subjects had quantifiable plasma concentrations as shown in Table 6.

Table 5: Systemic concentrations in subjects with measurable HBP plasma concentrations on Day 15

Subject	%BSA Affected at Baseline	%BSA Treated at Baseline	Amount Used† (mg/cm^2)	Day 15 HBP Plasma Concentration (pg/mL)	Day 15 Post-Serum Cortisol Level (µg/dL)
(b) (6)	11	11	0.48	35.8	7.2*
	20	15	1.23	29.7	21.4
	17	17	1.78	20.9	14.5*
	18	18	1.13	32.9	21.9
	23	20	0.95	22.4	17.4*
	18	18	0.81	299	28.4
	22	20	1.13	50.7	19.2
	11	10	1.68	23.8	23
	12	10	1.41	23.8	26.1

*HPA axis suppression was noted
Source: Sponsor's submission Table 12.6-1

Table 6: Summary of subjects with HPA axis suppression on Day 15

Subject	%BSA Affected at Baseline	%BSA Treated at Baseline	Amount Used† (mg/cm^2)	Day 15 HBP Plasma Concentration (pg/mL)	Day 15 Post-Serum Cortisol Level (µg/dL)
(b) (6)	11	11	2.01	<(20.0)	16.1*
	12	12	1.71	<(20.0)	12.6*
	11	11	0.48	35.8	7.2*
	17	17	1.78	20.9	14.5*
	23	20	0.95	22.4	17.4*
	12	12	1.68	<(20.0)	17.5*

*HPA axis suppression was noted
Source: Sponsor's submission Table 12.1-1

Summary of efficacy: The main objective of this study was to assess safety, not efficacy. Also, this is an open label study and hence efficacy results are considered as exploratory. By Day 15, all but 1 subject (95.5%) had improvements in IGA by at least a 1-point shift. Subject (b) (6) did not show any change from Baseline in IGA nor percent BSA affected and/or treated. There were 72.7% (16/22) of subjects with at least a 2-point change (improvement) from Baseline in IGA on Day 15 (2-point: 11/22, 50%; 3-point: 5/22, 22.7%). Overall, the mean percent BSA affected with disease decreased from 15.1% at Baseline to 9.1% by Day 15 and the mean percent BSA treated decreased from 14.5% at Baseline to 12.6% by Day 8.

Summary of Safety: There were no deaths, serious adverse events (AEs) or discontinuation of treatment due to AEs. A total of 7 subjects (7/24, 29.2%) reported 8 treatment emergent adverse events (TEAEs). Of the 8 TEAEs, 6 were deemed related (ACTH stimulation test abnormal) and 2 were deemed not related (gastritis and red blood cells urine positive) to HBP Foam. All but 1 TEAE (moderate gastritis) were mild in severity. None of the TEAEs were serious, none were within the Treatment Area, none required a change in test article dosing or discontinuation from the study, and all TEAEs recovered/resolved by EOS.

Subjects who had Adrenal Suppression at Day 15: Post treatment, 6 out of 23 (26.1%) of subjects showed HPA axis suppression as indicated by post stimulation cortisol levels of ≤ 18 µg/dL. All the six subjects had a follow up CST done at least 4 weeks after the last dose on Day 15 and the cortisol levels returned to normal and none of the subjects demonstrated any clinical signs or symptoms of adrenal suppression as shown in Table 7 below.

Table 7: Follow-up of subjects with adrenal suppression at Day 15

Subject	Screening/Baseline Post-CST Cortisol (µg/dL)	Day 15 Post-CST Cortisol (µg/dL)	Follow-Up (~4 weeks after Day 15) Post-CST Cortisol (µg/dL)	Total Test Article Used (grams)
(b) (6)	30.1	16.1*	23.9	124.4
	24.8	12.6*	21.2	94.8
	23.6	7.2*	34	20.1
	23.8	14.5*	25.4	115.4
	18.1	17.4*	26.4	84.4
	26.4	17.5*	25.6	74.5

Source: Sponsor's submission Table 12.5-1

Summary of local skin reactions: Burning/stinging and folliculitis were absent for all subjects at all visits. With the exception of 1 case of severe telangiectasia at Baseline prior to test article application, all other cases of telangiectasia and skin atrophy were moderate or mild in severity during the study. Telangiectasia and skin atrophy were observed in 6 subjects.

Summary of bioanalytical method validation:

Halobetasol propionate: (b) (4). developed a validated liquid chromatographic-mass spectrometry (LC-MS/MS) method to analyze human plasma samples. β-Estradiol was used as an internal standard. The plasma samples were stored at -20°C until analysis. Long term storage stability was determined to be 532 days at -20°C and this was deemed adequate. The freeze-though stability for up to 3 cycles was determined. Bench top stability was at least 17 hours and at least 92 hours at 5°C.

The linear concentration range was 20 pg/mL to 4000 pg/mL (mean R-square was 0.9921). Summary of precision and accuracy of the bioanalytical method for the determination of HBP in human plasma is shown in the Table 8 below. The QC sample acceptance criteria was at least 67% of all QC samples are within ± 15% of their respective nominal concentrations (± 20% at LLOQ).

Table 8: Summary of bioanalytical method validation

Watson Run ID	Nominal Concentration QC LLOQ 20.0 pg/mL	QC Low 60.0 pg/mL	QC Mid 600 pg/mL	QC High 3000 pg/mL
6	22.1	57.0	557	3150
	18.8	55.3	558	3310
	20.1	58.0	554	3600 [a]
	20.7	49.3 [a]	581	2720
	18.9	53.3	596	2670
	17.6	51.6	544	2760
Mean	19.7	54.1	565	3040
S.D.	1.60	3.32	19.5	378
%CV	8.1	6.1	3.5	12.4
%Bias	-1.5	-9.8	-5.8	1.3
n	6	6	6	6

[a] = Value outside of acceptance criteria (± 15% theoretical) but included in summary statistics.

Source: Report No. 037664

Incurred sample reanalysis: Of the 80 specimen samples that were analyzed for HBP, Incurred Sample Reanalysis (ISR) was performed on eight of these samples for a total of 10% of all samples analyzed. In order for the ISR to be successful, at least 2/3 (or 67%) of the reanalysis results must be within ±20% of mean of the original and reanalysis results.

The first ISR run failed with only 3 of 8 (37.5%) reanalyzed samples were within ±20% of the mean of the original and reanalysis result. The Applicant conducted an investigation to determine the root cause of the ISR failure and identified some methodological issues. The investigation led to the performance of a second ISR run and the results showed that 6 of 8 (75.0%) ISR samples were within ±20% of the mean results. The ISR results shown in Table 9 are acceptable.

Table 9: ISR Results

Study 037664-Clinical SA of Halobetasol Propionate in Human K_3EDTA Plasma using LC-MS/MS Analysis
Mandatory Repeat Report
Concentrations of Halobetasol Derivative in Plasma (pg/mL)
(Repeat - Original)/(Mean) x 100 = %Bias

(b) (4) ID	Sample ID	Final Analysis Run ID	Final Original Concentration	Repeat Run ID	Repeat Concentration	%Bias	Flag
35	038090000035 23-001 8 Plasma-1 Day 8 / Day 8	5	87.3	9	94.8	8.2	
38	038090000038 23-002 8 Plasma-1 Day 8 / Day 8	5	975	9	861	-12.4	
64	038090000064 32-005 15 Plasma-1 Day 15 / Day 15	17	29.0	16	34.6	17.5	
65	038090000065 32-005 8 Plasma-1 Day 8 / Day 8	17	30.8	16	39.9	25.9	>20
79	038090000079 32-010 15 Plasma-1 Day 15 / Day 15	17	299	16	303	1.4	
85	038090000085 32-012 15 Plasma-1 Day 15 / Day 15	17	50.7	16	52.2	2.8	
86	038090000086 32-012 8 Plasma-1 Day 8 / Day 8	17	47.1	9	49.0	4.0	
91	038090000091 33-002 15 Plasma-1 Day 15 / Day 15	17	23.8	16	33.6	34.0	>20
	ISR success rate (%)	75.0					

Source: Report No. 037664

Serum cortisol: [redacted] (b) (4)) were responsible for measuring cortisol in serum samples from subjects undergoing the adrenocorticotropic hormone (ACTH) challenge. Human serum cortisol analyzed using The Siemens ADVIA Centaur XP. The serum samples were stored at ≤ - 60°C and all samples were analyzed within the defined stability for serum cortisol.

The ADVIA Centaur is an automated analytical system that performs the cortisol assay. The automated system will initially dispense sample into a cuvette (20 µL). This is followed by Lite Reagent (50 µL) and Solid Phase (250 µL) and incubating for five minutes at 37°C. The system will then separate, aspirate, and wash cuvettes with reagent water. Following The wash cycle, the automated system will dispense Acid Reagent (300 µL) each and Base Reagent (300 µL) to initiate the chemiluminescent reaction.

An inverse relationship exists between the amount of cortisol present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Prior to analysis, a valid calibration was obtained. A calibration is valid for 10 days; however, the sponsor conducted additional calibration following changes to lot numbers of primary reagent packs, a need to replace system components, maintenance procedures or if quality control results were repeatedly out of range.

Quality Controls were analyzed with each analytical run and the results were assessed relative to the acceptance criteria. The results are shown in Table 10. The analytical measuring range of the assay is 0.2 - 75 µg/dL.

Table 10: Quality control for serum cortisol

	QC Level 1* (ug/dL)					QC Level 2* (ug/dL)					QC Level 3* (ug/dL)			
Month/Year	Target Mean	Running Mean	%Bias	Comments		Target Mean	Running Mean	%Bias	Comments		Target Mean	Running Mean	%Bias	Comments
Jun-19	5.504	5.732	4.142	Lot 40961		25.481	25.070	-1.613	Lot 40962		36.543	36.306	-0.649	Lot 40963
Jul-19	5.504	5.677	3.143	Lot 40961		25.481	24.964	-2.029	Lot 40962		36.543	35.872	-1.836	Lot 40963
Aug-19	5.504	5.270	-4.251	Lot 40961		25.481	24.443	-4.074	Lot 40962		36.543	35.077	-4.012	Lot 40963
Sep-19	5.504	5.529	0.454	Lot 40961		25.481	24.008	-5.781	Lot 40962		36.543	34.935	-4.400	Lot 40963
Oct-19	5.504	5.374	-2.362	Lot 40961		25.481	24.669	-3.187	Lot 40962		36.543	34.959	-4.335	Lot 40963
Nov-19	5.504	5.571	1.217	Lot 40961		25.481	25.273	-0.816	Lot 40962		36.543	36.025	-1.418	Lot 40963
Dec-19	4.500	4.469	-0.684	Lot 41001		23.816	23.314	-2.107	Lot 41002		35.720	35.033	-1.922	Lot 41003

* Each QC pack is supplied with three QC levels where each component has a sub-lot number.
QC Pack 40960 has three levels identified as 40961, 40962 and 40963
QC Pack 41000 has three levels identified as 41001, 41002 and 41003

Source: ACM Study Number: CY2447 392/655

3. DETAILED LABELING RECOMMENDATIONS

The following changes are recommended in the Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer, and the double ~~strikethrough~~ text indicates recommended deletion

5.1 Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Adverse Endocrine Effects

LEXETTE is a topical corticosteroid that has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression, with the potential for glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment of the topical corticosteroid. The potential for hypothalamic-pituitary adrenal (HPA) suppression with LEXETTE was evaluated in the following studies:

- In a study of 25 adult subjects with moderate to severe plaque psoriasis involving ≥15% of their body surface area. LEXETTE produced laboratory evidence of HPA axis suppression when used twice daily for two weeks in 6 out of 25 (24%) adult subjects with plaque psoriasis. **All subjects returned to normal HPA axis function at follow-up at least 4 weeks after stopping the treatment** (b) (4) [redacted] [see *Clinical Pharmacology (12.2)*].
- In another clinical study, 24 adolescent subjects (12 to less than 18 years old) with stable plaque psoriasis involving 10% or more of their body surface area applied **LEXETTE** (b) (4) to affected areas twice daily for two weeks. Of the 23 subjects evaluated for HPA axis suppression, laboratory evidence of adrenal suppression occurred in 6 subjects (26.1%), whom recovered upon (b) (4) **retesting after at least 4 weeks of stopping the treatment** *[see Clinical Pharmacology (12.2)]*.

Because of the potential for systemic absorption, use of topical corticosteroids, including LEXETTE, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, prolonged use, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to topical corticosteroids.

Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see *Use in Specific Populations (8.4*].

8.4 Pediatric Use

The safety and effectiveness of LEXETTE (b) (4) for the treatment of stable plaque psoriasis in pediatric subjects (12 to less than 18 years of age) is supported by evidence from adequate and well-controlled studies in adults and from one open label safety study in 24 adolescents. Adolescent subjects with stable plaque psoriasis covering a minimum of 10% of the total body surface area **at baseline** were treated twice daily for 2 weeks with LEXETTE (b) (4). Hypothalamic-pituitary adrenal (HPA) axis function (ACTH stimulation test) was evaluated in a subset of 23 subjects. After 2 weeks of treatment, 6 of 23 subjects (26.1%) experienced laboratory evidence of adrenal suppression (i.e., cortisol serum level of ≤18 μg/dL) that recovered upon (b) (4) **retesting after at least 4 weeks of stopping the treatment** [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.2)*].

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see *Warnings and Precautions (5.10)]*.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [see *Warnings and Precautions (5.10)]*.

12.2 Pharmacodynamics

Vasoconstrictor Assay

A vasoconstrictor assay in healthy patients with Halobetasol Propionate Foam, 0.05% indicated that the formulation is in the super-high range of potency as compared to other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

Hypothalamic-pituitary adrenal (HPA) axis suppression

The potential for hypothalamic-pituitary adrenal (HPA) suppression was evaluated in the following two studies. In both studies, the criteria for HPA-axis suppression was a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin (adrenocorticotropic hormone, ACTH).

In the first study, LEXETTE (b) (4) was applied to 25 adult subjects with moderate to severe plaque psoriasis involving a mean body surface area of 18.4%. A mean dose of 3.7 g LEXETTE was applied twice daily for two weeks and produced laboratory evidence of HPA axis suppression in 6 of 25 (24%) subjects. **All subjects returned to normal HPA axis function at follow-up at least 4 weeks after stopping the treatment** (b) (4) [see *Warnings and Precautions (*5.1*)*].

In the second study, LEXETTE foam was applied to 24 adolescent subjects 12 to less than 18 years of age with stable plaque psoriasis with a mean percent BSA of 15.1% (range of 11% to 23%). The mean dose of LEXETTE used was 3.1 grams, which was applied twice daily for two weeks. In the study, 24 subjects completed the study, and 23 subjects had evaluable ACTH stimulation tests. HPA axis suppression was observed in 6 of the 23 subjects (26.1%), **and all subjects returned to normal HPA axis function at follow-up at least 4 weeks after stopping the treatment** (b) (4) *[see Use in Specific Populations 8.4].*

12.3 Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

In the HPA-axis and pharmacokinetic study, as described above in *Clinical Pharmacology (12.2)*, pharmacokinetics was evaluated in a subgroup of 23 adult subjects with moderate to severe plaque psoriasis following twice daily treatment for 14 days with a mean daily dose of 7.4 g. Plasma concentration of halobetasol propionate **(HBP)** was measurable in all subjects and steady state was achieved by Day 14. The mean (± standard deviation) C_{max} concentration for LEXETTE on Day 14 was 199.7 ± 217.3 pg/mL, with the corresponding median T_{max} value of 1 hour (range 0 – 12 hours); mean area under the halobetasol propionate concentration versus time curve over the dosing interval (AUC_t) was 1434.9 ± 1310.6 pg•h/mL.

In the **adolescent** (b) (4) HPA study *[see Clinical Pharmacology (12.2)]*, trough plasma concentrations of HBP were measured on Day 8 and Day 15 in 23 subjects. At Day 8, (b) (4) **9** of the 23 evaluable subjects had morning trough concentrations of halobetasol propionate in plasma that were above the quantifiable limit (≥20.0 pg/mL); mean halobetasol concentration was **154.6** (b) (4) ± **308.67** (b) (4) pg/mL. Similarly, at Day 15, (b) (4) **9** of the 23 evaluable subjects had morning trough concentrations of halobetasol propionate above the quantifiable limit; mean halobetasol concentration was **59.9** (b) (4) ± **90.15** (b) (4) pg/mL. Of the **9** ~~10~~ subjects with quantifiable plasma concentrations at Day 15, seven (7) also had quantifiable plasma concentrations at Day 8.

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