Office of Clinical Pharmacology Review

NDA Number	022563
Submission Date(s)	10/01/2018 (SDN 322) – Refused to file 01/04/2019 (SDN 339) – Resubmission 04/19/2019 (SDN 354) 07/25/2019 (SDN 365) 08/26/2019 (SDN 368)
Submission Type	Efficacy Supplement (S-007)
Brand Name	SORILUX
Generic Name	Calcipotriene
Dosage Form and Strength(s)	Aerosol form, 0.005%
Route of Administration	Topical
Proposed Indication	Topical treatment of plaque psoriasis of the scalp and body
Applicant	Mayne Pharma LLC
Associated IND	071198
Primary Reviewer	Soo Hyeon Shin, Pharm.D., Ph.D.
Secondary Reviewer	Chinmay Shukla, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Dermatology and Dental Products

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1. EXECUTIVE SUMMARY

SORILUX (calcipotriene) Foam, 0.005% is approved for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older. The current efficacy supplement was submitted to fulfill a post-marketing requirement (PMR) 1944-3 and to seek an extended indication to younger pediatric patients.

The Applicant conducted Study STF115469, which was an open-label, multicenter study to evaluate the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of calcipotriene foam, 0.005%, in pediatric subjects with plaque psoriasis. The PMR was originally established to evaluate subjects aged 2 years to 11 years and 11 months and with at least 25 evaluable subjects for PK under maximum use conditions. However, due to difficulty recruiting subjects because of psoriasis being less common in younger subjects, the study was conducted in subjects 4 years and older and in fewer subjects (36 subjects), than initially planned (50 evaluable subjects).

1.1 Recommendations

The Office of Clinical Pharmacology finds the NDA 022563/S-007 acceptable.

1.2 Post-Marketing Requirements/Commitments

None

2. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

2.1 Overall study design (Study STF115469)

Objectives of the study

The primary objective was to evaluate safety by assessing adverse events, vital signs, and local tolerability. The secondary objectives were 1) to evaluate the PD effect (i.e. calcium metabolism), 2) to describe the plasma concentrations of calcipotriene and 3) to describe the treatment effect of calcipotriene foam, 0.005% in pediatric subjects with mild to moderate plaque psoriasis.

Study subjects

This study conducted in a total of 36 subjects aged 4 years to less than 12 years with mild to moderate plaque psoriasis. Key inclusion criteria relevant to Clinical Pharmacology standpoint included subjects with at least moderate plaque psoriasis (Investigator's Static Global Assessment [ISGA] score of or 3) and % body surface area (BSA) involvement of at least 3% with some scalp involvement.

Dosing regimen

Subjects were instructed to apply a thin layer of study product to treatment areas affected by plaque psoriasis (except the face) in the morning and in the evening for 8 weeks.

Reviewer's comment: *Due to difficulty recruiting subjects, there has been multiple changes to the study protocol and subjects were enrolled under different versions of protocol with different enrollment criteria and PK and PD assessment timepoints. In addition, there were several missing data for some subjects which included for example, missing PK and PD assessments, missing dosing compliance information, etc. The Clinical Pharmacology review team along with the Clinical review team had to carve out subjects that provided sufficient information that helped in the decision-making for this supplement. The details of these subjects can be found in Appendices 1 and 2 for the PK and PD populations, respectively.*

2.2 Pharmacokinetics

Blood samples for PK assessment of calcipotriene were collected at Baseline (Week 1), Week 2 and Week 8. PK data was collected from a total of 16 subjects, including two who received vehicle formulation. All samples analyzed had calcipotriene concentrations below the limit of quantification (LOQ) (10 pg/mL). Subject demographic information is shown in Appendix 1.

Reviewer's comments*: Only 11 out of 16 subjects were determined to have sufficient data to inform the systemic safety of SORILUX and were included in data analysis for review. The mean age of these 11 subjects was 9.9 years (range: 7-11 years, median: 9.5 years). Given that the bioanalytical method was reasonably sensitive with the LOQ in the sub-nanomolar range (10 pg/mL = 0.023 nM), it appears that the systemic absorption of calcipotriene from SORILUX in pediatric subjects down to 7 years old is minimal.*

2.3 Pharmacodynamics – Effects on calcium metabolism

The study evaluated albumin adjusted calcium, iPTH, alkaline phosphatase, magnesium, and phosphorus along with the urine calcium/creatinine ratio as measures of the effect of SORILUX on calcium metabolism. These PD markers were measured at Screening, Baseline (Week 1), Week 2 and Week 8. The submitted PD data were obtained from 23 subjects, including two who received vehicle formulation.

Reviewer's comments*: Among 23 subjects identified as the PD population per the Applicant, 18 subjects were determined to have sufficient urine calcium/creatinine ratio data to inform the potential PD effects of SORILUX. Subject demographic information and urine calcium/creatinine ratio are shown in Appendix 2 and Appendix 3, respectively. The mean age of these 18 subjects was 9.7 years (range: 5-11 years, median: 9.5 years). With regard to the potential concern with hypercalcemia, two subjects (Subject IDs* [redacted] *) out of 18 subjects in the PD population had an elevated calcium/creatinine ratio outside the normal range at Week 8. However, Subject* [redacted] *'s value was only slightly higher than the upper limit of the reference range (245 vs 240 mg/g creat), while the value in subject* [redacted] *was 285. Both subjects did not experience adverse events that were related to SORILUX. Based on the totality of data in addition to the lack of clear correlation between urine calcium/creatinine ratio and the*

presence of hypercalciuria (or urinary calcium excretion measured by a 24 hr urine collection)[1]*, it was determined that there is no clinically significant effect on indices of calcium metabolism. See Clinical review by Dr. Melinda McCord for additional information on safety.*

2.4 Bioanalytical methods

To determine calcipotriene concentration in plasma, a validated liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS) was used. The bioanalytical assay and the method validation are acceptable. Incurred sample reanalysis was not conducted due to insufficient samples and all samples being below the LOQ. All samples were analyzed within 633 days, which is within the established stability period of 1821 days at -60 to -80° C.

To determine calcium concentrations in serum and urine, a commercially available system reagent that is of a cleared 501(k) application was used which is acceptable.

[1] Choi S, et al. Random urinary calcium/creatinine ratio for screening hypercalciuria in children with hematuria. Ann Lab Med. 2013 Nov; 33(6):401-405.

3. APPENDICES

Appendix 1. Demographics of the PK Population from Study STF115469

ID	Age	Sex	Race	% BSA Involvement at Baseline	ISGA Score at Baseline – Scalp	ISGA Score at Baseline – Body	% Compliance – Scalp	% Compliance – Body	Average Daily Dose
(b) (6)	7	F	White	26	2	2	100	100	12.95
	9	M	Black or African American	21	3	3	100	100	17.17
	9	M	White	17.51	4	3	100	100	4.26
	10	M	White	19.9	3	4	100	100	7.46
	10	F	Black or African American	7	3	3	100	100	11.86
	10	F	White	26	3	3	56.43	95	19.81
	10	M	White	7	2	2	96.43	96.43	4.91
	11	F	White	7	2	2	100	100	4.75
	11	F	Black or African American	13.4	4	4	-	-	-
	11	M	White	36.5	1	3	100	100	8.63
	11	F	White	8.5	3	2	99.12	99.12	6.84
Mean	9.9	F: 55%	White: 73%	17.3	2.7	2.8	95.2	99.1	9.9
Median	10.0			17.5	3.0	3.0	100.0	100.0	8.0
SD	1.2	M: 45%	Black or African American: 27%	9.8	0.9	0.8	13.7	1.8	5.4
n	11			11	11	11	10	10	10

Appendix 2. Demographics of the PD Population from Study STF115469

ID	Age	Sex	Race	% BSA Involvement at Baseline	ISGA Score at Baseline – Scalp	ISGA Score at Baseline – Body	% Compliance – Scalp	% Compliance – Body	Average Daily Dose
(b) (6)	5	F	White	14	2	2	-	-	14.6
	6	F	White	-	3	0	100	-	3.7
	7	M	White	2.5	0	2	100	100	4.4
	7	M	Other	-	0	2	100	-	3.1
	8	F	White	-	3	0	100	-	1.3
	9	F	White	6	2	3	100	100	10.9
	9	M	White	6	0	3	100	100	0.5
	9	F	White	-	3	3	100	0	-
	9	M	White	17.51	4	3	100	100	4.3
	10	M	White	19.9	3	4	100	100	7.5
	10	M	Black or African American	3	0	2	93.75	100	3.6
	10	F	Black or African American	7	3	3	100	100	11.9
	10	M	White	7	2	2	96.43	96.43	4.9
	10	M	Other	2.5	3	2	83.04	83.93	11.2
	11	M	White	14	3	4	100	100	14.5
	11	F	White	0.5	1	3	100	100	0.3
	11	M	White	36.5	1	3	100	100	8.3
	11	F	White	8.5	3	2	99.12	99.12	6.8
Mean	9.1	F: 44%	White: 78%	10.4	2.0	2.4	98.4	91.4	6.6
Median	9.5	M: 56%	Other: 11%	7.0	2.5	2.5	100	100	4.9
SD	1.8		Black or African American: 22%	9.6	1.3	1.1	4.3	26.7	4.6
n	18			14	18	18	17	14	17

Appendix 3. Urine Calcium/Creatinine Ratio of the Qualified PD Population from Study STF115469

ID	Age	Sex	Ca/Cr Ratio at Screening (mg/g creat)	Ca/Cr Ratio at Baseline (mg/g creat)	Ca/Cr Ratio at Week 2 (mg/g creat)	Ca/Cr Ratio at Week 8 (mg/g creat)
(b) (6)	5	F	103	55	50	112
	6	F	19	100	121	-
	7	M	53	33	102	103
	7	M	172	218	220	245 [a]
	8	F	48	42	32	-
	9	F	77	21	30	35
	9	M	66	20	60	110
	9	F	117	286	91	140
	9	M	40	19	45	34
	10	M	96	160	141	40
	10	M	40	10	30	17
	10	F	-	7 [b]	13	17
	10	M	-	52	52	285 [a]
	10	M	45	15	84	128
	11	M	57	50	61	133
	11	F	88	36	-	49
	11	M	152	14	150	179
	11	F	-	7 [b]	7 [b]	37

Reference range for female subjects: 10-320 mg/g creat

Reference range for male subjects: 10-240 mg/g creat

[a] Outside the upper limit of reference range

[b] Outside the lower limit of reference range

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/s/

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