CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-087

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	8 January 2009
From	Jill A Lindstrom, MD
Subject	Cross-Discipline Team Leader Review
NDA #	22-087
Applicant	Galderma
Date of Submission	21 Dec 07
PDUFA Goal Date	27 Jan 09 (originally 27 Oct 08, extended following submission of major amendment)
Proprietary Name / Established (USAN) names	Vectical/calcitriol
Dosage forms -- Strength	Ointment -- 3mcg/gm
Proposed Indication(s)	Topical treatment of mild to moderate psoriasis in adults
Recommended:	*Approval*

1. Introduction

Vectical (calcitriol) Ointment, 0.003%, is a topical vitamin D analogue for which the sponsor seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of psoriasis in adult patients. This memo will summarize the findings of the multi-disciplinary review team and highlight my recommendations for labeling.

2. Background

Vectical (calcitriol) Ointment, 3mcg/g, was initially registered in Switzerland on April 27, 1995 under the tradename Silkis, and is currently marketed with that name by the applicant in 42 countries for the treatment of psoriasis. The active moiety, calcitriol, is marketed (by other sponsors) in the United States as an oral tablet, oral solution, and solution for injection, for treatment of other indications.

The application is a resubmission of an application submitted but not filed in September 2006. The Agency refused to file the application at that time because it contained inadequate data to support the proposed manufacturing site; this information was provided in the current application.

3. CMC

The drug substance, calcitriol, is also known as 1α,25-dihydroxycholecaciferol, 1α,25-dihydroxyvitamin D_3, and 1,25-$(OH)_2D_3$. It is a white, crystalline powder. Calcitriol is sensitive to oxidants and light exposure. The drug substance is marketed in the US as an oral tablet, an oral solution, and solution for injection.

The drug product, calcitriol ointment 3mcg/gm, is a white, translucent semi-solid ointment containing the active ingredient calcitriol and the excipients petrolatum, mineral oil, and dl-α-

tocopherol. Calcitriol is fully solubilized in the formulation. The composition is described in the following table:

Ingredient	Percent Formula (%w/w)	Function
Calcitriol	0.0003	Active ingredient
White petrolatum	[redacted]	
Mineral oil		
dl-α-tocopherol		

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Source: adapted from CMC review of NDA 22-087, Dr. Jane Chang, 10/9/2008, p34.

The drug product is packaged in [redacted] aluminum tubes with [redacted] screw caps. The applicant submitted data for tube sizes of 5g, [redacted] and 100g, but intends to market only the 100g size and supply the 5g size as physician samples. Stability data supports an expiry of 36 months.

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Facilities inspections for the drug substance [redacted] and drug product (Canada) were satisfactory from the perspective of both ONDQA and the Office of Compliance.

The CMC reviewer, Dr. Jane Chang, recommends *Approval* of this application.

An unresolved issue related to CMC is labeling, specifically the nomenclature for the excipient dl-α-tocopherol, or vitamin E. This is addressed later in this review in Section 11, Labeling.

4. Nonclinical Pharmacology/Toxicology

The applicant conducted the following repeat dose toxicology studies: a 13-week oral (gavage) study in rats; 13 week topical (dermal) study in hairless mice (with and without ultraviolet radiation), 13 week dermal toxicity study in minipigs, 13 week dermal study in beagle dogs, 26 week dermal study in rats, and a 9-month dermal toxicity study in minipigs. The primary manifestations of toxicity were perturbations in calcium homeostasis such as elevations of calcium and phosphorus in serum and urine, hyperostosis, and mineralization of the kidney and other tissues. These toxicities were primarily seen in the oral studies and in topical studies in which oral ingestion occurred. Dermal absorption appeared to be low. In the 9-month dermal toxicity study in mini-pigs, the NOAEL occurred with the 3ppm calcitriol ointment (the formulation and concentration proposed for marketing), and the [redacted] ointment induced minimal toxicity.

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Calcitriol was not found to be mutagenic nor carcinogenic. However, in a 12-month photococarcinogenicity study, both Vectical ointment and vehicle ointment caused a reduction in time to tumor formation compared to untreated animals, suggesting that the vehicle enhances UV-induced tumor formation, possibly through increasing UV penetration of the skin. This is addressed in labeling.

Calcitriol did not reduce fertility in male or female rats. Calcitriol was found to be fetotoxic in rabbits but not rats; abnormalities included minor skeletal abnormalities, which Dr. See considered likely secondary to maternal toxicity. This is addressed in labeling.

There are no outstanding nonclinical pharmacology/toxicology issues. Dr. See recommended *Approval* from the pharmacology/toxicology perspective. No nonclinical postmarketing studies are recommended or required.

5. Clinical Pharmacology/Biopharmaceutics

Calcitriol is an endogenous molecule. Calcitriol is marketed as an oral tablet, oral solution, and solution for injection. The applicant's formulation is an ointment for topical administration.

The applicant conducted a maximal use systemic exposure (MUSE) study (Study 40005) in psoriatic subjects with a minimum body surface area involvement of 25%, and up to 35%; all subjects applied 15gms of study drug BID to 35% BSA (up to 10% BSA normal skin). In my opinion, 35% BSA reasonably represents the upper end of usage likely to be encountered during marketing; topical treatment of greater than 15% BSA by psoriasis patients is often impractical as it is time-consuming and cumbersome to apply topical medication to such extensive areas of the skin. As described in the Clinical Pharmacology review by Dr. Ghosh, the geometric mean values for C_{max} of calcitriol in the MUSE study increased by approximately 36% over baseline. For context, from the Rocaltrol package insert, the mean serum concentrations of calcitriol increased by approximately 50% over baseline following oral administration of Rocaltrol[1]; however, these data are from separate studies involving dissimilar populations conducted at different times, so direct comparisons are difficult; additionally, the applicant did not conduct bridging studies to any approved product. In the MUSE study conducted by the applicant, no correlation was observed between pharmacokinetic parameters (C_{max} or AUC) and pharmacodynamic measures (albumin-adjusted serum calcium, serum phosphorus, urinary calcium, and urinary phosphorus). This suggests that the feedback mechanisms for calcium homeostasis are sufficiently plastic to accommodate the exogenous calcitriol systemically absorbed following treatment with the applicant's product without causing significant perturbations in serum or urine calcium or phosphorus.

The applicant did not conduct a thorough QT/QTc study. The Guidance for Industry document *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* states that the "...document is concerned primarily with the development of novel agents,...[or] approved drugs when a new dose or route of administration is being developed that results in significantly higher exposure (i.e., C_{max} or AUC)." Calcitriol is not a new molecular entity; it has been marketed as an oral capsule since 1978 and as a solution for injection since 1986. Although the applicant did not conduct a

[1] Rocaltrol package insert, CLINICAL PHARMACOLOGY: Pharmacokinetics section; labeling approved 7/27/2004.

bridging study, the applicant's product resulted in a smaller increase in Cmax relative to the increase in Cmax reported in the package insert for oral calcitriol, suggesting that the topical formulation does not result in a significantly higher exposure than the oral formulation. Pharmacokinetic data are not included in the package insert for the injectable formulation (Calcijex), but it is unlikely that the 1mcg dose for injection would be less bioavailable than the same dose orally administered, which appears to exceed the exposure of the topical product. Additionally, as an endogenous compound, it is unlikely that calcitriol would delay cardiac repolarization. Finally, although not a compelling argument, the AERS database did not reveal a signal for cardiac conduction adverse events. The applicant's rationale is discussed in the clinical review by Dr. Trish Brown.

The clinical pharmacology reviewer, Dr. Tapash Ghosh, recommended *Approval* of the NDA.

6. Clinical Microbiology

Not relevant.

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, Study 18053 and Study 18054, to establish the effectiveness of their product applied twice daily for 8 weeks in the treatment of psoriasis. These trials (18053 and 18054) were multi-center, prospective, randomized, double-blind, parallel group studies with two arms, active and vehicle. The population enrolled was subjects 12 years of age and older with mild to moderate psoriasis (investigator global assessment score of 2 or 3) at baseline and not greater than 35% body surface area involvement.

The applicant attended an EOP2 meeting on November 15, 1999, at which the following comments were made regarding the primary efficacy parameters proposed in the protocol synopses:

- Clinical: "The investigator's global assessment dichotomized to success/failure is recommended. Success is recommended to include only clear or almost cleared,"
- Biostatistics: "the Division recommends the dichotomized static global assessment as a primary efficacy variable in the Phase 3 trials."

The applicant did not request a special protocol assessment, and no agreement letter was issued.

The primary efficacy measure was the investigator's global assessment (IGA), assessed using the Global Severity Scale (GSS). The primary timepoint was at 8 weeks, and the primary endpoint was the proportion of subjects with success, defined as Clear or Minimal, on the GSS.

The efficacy results from the pivotal trials are presented in the table below, both the primary endpoint specified by the applicant (clear or minimal, but allowing a one-grade improvement) and reanalyzed by the biostatistician using the definition of success, clear or minimal *and* a two-grade improvement) that would ensure clinical meaningfulness.

Definition of Success	Study 18053		Study 18054	
	Calcitriol (N=209)	Vehicle (N=209)	Calcitriol (N=210)	Vehicle (N=211)
Clear or Minimal, 1-gr. improvement allowed	72 (34.4%)	47 (22.5%)	70 (33.3%)	26 (12.3%)
p-value*		0.0047		<0.001
Clear or Minimal *and* 2-gr. improvement	49 (23.4%)	30 (14.4%)	43 (20.5%)	14 (6.6%)
p-value*		0.0142		<0.001

*p-values are based on CMH stratified by pooled site.
Source: adapted from Statistical Review and Evaluation, NDA 22-087; Dr. Mat Soukup, archived 9.18.08, p.10.

The need for a two-grade improvement to ensure a clinically meaningful difference is intrinsic to the use of an investigator's global assessment scale, a categorical scale imposed upon a continuous variable. Without the requirement for a two-grade improvement, a subject with baseline disease that represented a "high two," (that is, an "almost-but-not-quite-a-one") who improved to a "low one" (that is, "almost-but-not-quite-a-two") would be classified as a success despite minimal improvement. A two-grade change ensures that subjects classified as success will have achieved clinically meaningful improvement, regardless of their baseline score. A two-grade improvement, if not intrinsic to the entry criteria (such as would be the case were enrollment limited to subjects with moderate or more severe disease, but which is not the case here), is the current labeling standard for endpoints based on a dichotomized investigator global scale, to ensure that prescribers can meaningfully interpret whether the potential benefit justifies the possible risk for their patients.

The applicant demonstrated the effectiveness of their product in the treatment of mild to moderate psoriasis when used twice daily for 8 weeks. Although the treatment effect is modest in both studies (~12% and ~21%, respectively, analyzed using the applicant's definition of success), it was replicated and it is present, albeit smaller (~9% and ~14%) when analyzed using the definition of success (two-grade improvement) that ensures clinical meaningfulness. Because of the modesty of the treatment effect, the absence of any preclusive agreements, the precedence in labeling of other products, and the current standard for labeling, the clinical studies section should include only the results that use the clinically-meaningful endpoint in which success is defined as clear or minimal and 2-grade improvement.

8. Safety

The safety database is adequate. In the controlled studies in which calcitriol was used as monotherapy, 1068 subjects were exposed to calcitriol dosed BID, including 419 subjects in

the pivotal trials (18053 and 18054). In uncontrolled studies, 849 subjects were exposed to calcitriol, including 324 in the open-label long term safety study (Study 2663).

One death occurred during the development program, but it was not considered related to Vectical use (autopsy revealed atheroma). There were no deaths in the pivotal studies or long-term safety study (2663), and there were also no serious adverse events (SAEs) attributable to study drug in these three studies. In the larger development program, two SAEs, erythema annulare centrifigum and worsening of psoriasis, were reported as related to study drug administration. The most frequently reported adverse event, both overall and related to Vectical use, was laboratory test abnormality. Collection of adverse event data and assessment of local tolerance did not reveal unexpected safety signals.

Three subjects from the open-label long-term safety study (2663) reported urinary stones (confirmed in two subjects); all three subjects had elevated 24-hour urine calcium at baseline. No subjects developed stones in the controlled pivotal studies. Two other subjects reported urinary stones during the development program, one of whom had a prior history of nephrolithiasis, and the other was diagnosed on study day 29, suggesting that the onset of the stone preceded initiation of study drug treatment. In these cases, the study design, presence of confounding factors, prior history, and/or time course do not allow for attribution of nephrolithiasis to use of the drug. The occurrence of urinary stones during the development program can be addressed in labeling.

Parameters of calcium homeostasis (calcitriol, serum albumin-adjusted calcium, serum phosphorus, urinary calcium, and urinary phosphorus) were assessed in the PK study (40005), a subset of subjects in the pivotal trials (18053 and 18054), and the long-term safety study (2663); calcitonin was not assessed. The results from study 40005 are discussed above; no correlation between pharmacokinetic and pharmacodynamic parameters was identified. In all of the studies, although minor perturbations in serum calcium were observed, no subject developed hypercalcemia above the threshold for concern (10% above the upper limit of normal). In the pivotal trials, group means for serum albumin-adjusted calcium and serum phosphorus were essentially unchanged at week 8 when compared with pretreatment values. The group means for serum PTH showed a small decrease at week 8 compared to pretreatment in both studies, but because the baseline PTH values (group means) were higher in the calcitriol arms, the decreased week 8 values were essentially the same for the active and vehicle arms in both studies, and were well within the reference range. In the long term safety study, group means for the parameters of calcium homeostasis (to include urinary calcium and urinary phosphorus from 24hour urine) were stable over the course of the study. The applicant provided an analysis of calcium-phosphate product. No subjects developed elevations of Ca-P product above the threshold for concern (5.6mmol/L). Although the data do not suggest that routine laboratory monitoring is needed, the risk for perturbations in calcium homeostasis should be addressed in labeling.

No postmarketing commitments or requirements to address safety concerns are warranted.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Calcitriol is not a new molecular entity.

10. Pediatrics

The applicant requested a partial waiver for the pediatric age group less than 2 years of age because the necessary studies would be highly impractical based on the small number and geographical dispersion of patients with psoriasis in that age group. The applicant requested a deferral for those 2 to 17 years of age. The applicant completed studies in adults.

Although additional studies are needed to establish the safety of Vectical Ointment in children prior to extension of the indication to the pediatric age group, the efficacy of Vectical Ointment can be extrapolated from adult data. Psoriasis vulgaris occurs in both children and adults, and although the disease prevalence varies with age, the pathophysiology is understood to be the same across all ages. Additionally, there are not known age-related factors that would make the disease either more or less responsive to treatment in pediatric patients (although there are unique factors in children that may increase their risk for adverse events, or increase the significance of those adverse events should they occur). Therefore it is scientifically appropriate to extrapolate efficacy from the adult population to the pediatric population, but the systemic safety of the product will need to be established for the pediatric age group 2-17 years of age.

The application was presented to the Pediatric Review Committee (PeRC) on October 22, 2008. The committee concurred with the Division's recommendation to grant a partial waiver for pediatric patients aged 0 to 2, and a deferral for pediatric patients aged 2 to 17. The committee agreed with the plan to conduct a PK/PD study in children with psoriasis, a vehicle-controlled safety and efficacy trial in subjects 2-12 years of age with psoriasis, and a long-term safety study in children, as detailed below:

1. The applicant should conduct a PK/PD study in 25 evaluable pediatric subjects with psoriasis aged 12 to 17, or in an adequate number to characterize the pharmacokinetics with sufficient precision.
2. The applicant should conduct a PK/PD study in pediatric subjects with psoriasis aged 2 to 12; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or a minimum of 25 evaluable subjects, whichever is larger.
3. The applicant should conduct a vehicle-controlled study of the safety and efficacy of their product in pediatric subjects with psoriasis aged 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to active.
4. The applicant should conduct long-term safety study of their product in 100 evaluable pediatric subjects aged 2 to 17 years of age.

The subjects in these studies should have careful monitoring of serum and urine parameters of calcium homeostasis, as well as parameters of bone metabolism.

5. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.
DMEPA did not find the tradename Vectical Ointment to be vulnerable to name confusion that could lead to medication errors, and did not object to its use.

6. Labeling

Labeling negotiations were ongoing at the time of closure of this review. The primary outstanding issue is nomenclature for the excipient dl-α-tocopherol. The applicant requested use of the monike[illegible] in both the package insert and the carton and container labels because it is the established name per the USP. However, the USP states that [illegible] which refers to a mixture, should be labeled to identify the isomer (in this case, dl-α-tocopherol) if the mixture is not used. More significantly, 21 CFR 201.10(c)(4) states that product labeling may be misleading, hence the product misbranded, if "...inert or inactive ingredients [are listed] in a manner that creates an impression of value greater than their true functional role in the formulation." Labeling the excipient as "[illegible] rather than as "dl-α-tocopherol" may mislead both patients and providers by implying that excipient is present in sufficient amounts to function either as a human vitamin or as a human antioxidant. In this formulation, dl-α-tocopherol does not function as a vitamin or as a human antioxidant. The applicant identified its function solely as an antioxidant for the product. No data was presented to substantiate any drug claims for dl-α-tocopherol. It is present in minute amounts [illegible] in the drug product; however this information (compositional percent) is not included in labeling or available to the public. To avoid misleading prescribers and patients regarding the contribution of the excipient dl-α-tocopherol to the product, this reviewer strongly advocates labeling the excipient as "dl-α-tocopherol" rather than as "[illegible] This will be consistent with foreign labeling submitted for this product, in which the excipient is variously identified as tocopherol, α-tocopherol, or dl-α-tocopherol, but never as "[illegible] Additionally, there is precedence for use of "tocopherol" rather than "[illegible] in the labeling for other products (e.g. Dovonex, Neupro) which contain tocopherol as an excipient, as detailed in the CMC review.

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7. Recommendations/Risk Benefit Assessment

I concur with the recommendations of the multi-disciplinary review team for approval of NDA 22-087, Vectical Ointment, pending agreement of the applicant with the recommended labeling revisions. The risk-benefit ratio for this product is appropriate for the indication of topical treatment of psoriasis in adults. Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance is not needed. However to fulfill the requirements of PREA, the applicant will need to study the safety and effectiveness of Vectical Ointment in pediatric subjects aged 2 to 17 years of age.

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/s/

Jill Lindstrom
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