

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-852

SUMMARY REVIEW

Secondary Review and acting Deputy Director Memo for NDA 21-852
Taclonex Ointment

Submission date: 3/9/05

CDER Stamp date: 3/11/05

Applicant: Leo Pharmaceutical Products Ltd..

Indication sought: topical treatment of psoriasis vulgaris in adults aged 18 years and above

The applicant has requested approval for Dovobet® Ointment, a combination product containing calcipotriene hydrate and betamethasone dipropionate, for the topical treatment of psoriasis vulgaris in adults aged 18 years and above. In support of this indication, the applicant has submitted results from a single pivotal trial and six supportive trials. The applicant proposed the tradename Dovobet, however the accepted tradename is Taclonex.

Efficacy

The applicant conducted a single pivotal trial, MCB 0003 INT to investigate the safety and efficacy of their product used once daily for four weeks in the treatment of psoriasis vulgaris. Additionally, results from six supportive studies were submitted; however, only four of these studies used dosing regimens comparable to that of the pivotal trial (qd for 4 weeks), and only two of those four included a static global assessment scale as an efficacy endpoint.

The pivotal trial was an international, multi-center, prospective, randomized, double-blind, parallel group study with four arms: Dovobet ointment, betamethasone in vehicle ointment, calcipotriol in vehicle ointment, and vehicle. After randomization in a 3:3:3:1 ration, 1603 subjects were applied their respective study drug once daily for four weeks. Primary endpoints included a static Investigator's Global Assessment (IGA) score dichotomized to success and failure and percent change in Psoriasis Area and Severity Index (PASI) score, assessed week 4. Table 1, below, from Dr. Mat Soukup's biostatistics review, describes the results for the IGA:

Table 1. Efficacy Results for Percent of Successes using the IGA* (ITT)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N.	490	476	480	157
Success (%)	276 (56.3%)	176 (37.0%)	107 (22.3%)	16 (10.2%)
p-value ¹		$p < .0001$	$p < .0001$	$P < .0001$

¹ p-value is the same for reviewer's analysis using CMH stratified by reviewer's definition of pooled center and for sponsor's logistic regression using sponsor defined pooled center.

Success is defined as 'very mild' or 'absence' of disease which is defined by the sponsor as 'controlled disease'.

Source: Statistical Review and Evaluation of NDA 21-852, p.5, Mat Soukup, PhD.

Using a more stringent definition for success, Absent or Mild Disease *and* a two-grade improvement on the IGA, the following results were achieved:

Table 2. Efficacy Results for Percent with Controlled Disease (2 Grade Improvement)

	Dovobet®	Betamethasone	Calcipotriol	Vehicle
N	490	476	480	157
Success (%)	235 (47.8%)	125 (26.3%)	79 (16.5%)	12 (7.6%)
p-value ²		<i>p</i> < .0001	<i>p</i> < .0001	<i>p</i> < .0001

¹ p-value is based upon reviewer's analysis using CMH stratified by reviewer's definition of pooled center.

Source: Statistical Review and Evaluation of NDA 21-852, p.15, Mat Soukup, PhD.

The results for the other primary efficacy endpoint, percent reduction in PASI, are described in Table 3:

Table 2. Efficacy Results for Percent Reduction in PASI: Study MCB-0003-INT.

	Dovobet® QD	Betamethasone QD	Calcipotriol QD	Vehicle QD
N	490	476	480	157
Mean (SD)	71.3% (25.7%)	57.2% (29.8%)	46.1% (30.9%)	22.7% (33.5%)
p-value ¹		<i>p</i> < .0001	<i>p</i> < .0001	<i>p</i> < .0001

¹ p-value is based upon reviewer's analysis using ANOVA with design variables for treatment and reviewer's definition of pooled center.

Source: Statistical Review and Evaluation of NDA 21-852, p.19, Mat Soukup, PhD.

The six non-pivotal studies were also supportive. Four of the six studies used percent change in PASI as primary endpoint and did not include a static IGA scale. However, in the pivotal trial, reduction in PASI correlated well with the stringent definition of controlled disease (Absent or Very Mild and 2 grade improvement on IGA), which allowed extrapolation of the percent change in PASI endpoint in the non-pivotal studies to be considered supportive for efficacy.

In summary, in their pivotal trial, the applicant demonstrated that Dovobet ointment applied once daily for four weeks is significantly superior to vehicle as well to each monad in the treatment of psoriasis. The robustness of the pivotal trial data, as well as the consistency of the results from the supportive studies (detailed in the excellent reviews by Drs. Brenda Carr and Mat Soukup), allow determination of efficacy with a single pivotal study.

Safety

The safety population included 2448 subjects with psoriasis vulgaris who were treated with Dovobet ointment, 1539 with once daily treatment and 909 with twice daily treatment. Systemic safety concerns with this combination product include HPA axis suppression and hypercalcemia.

The effect of Dovobet treatment on the HPA axis was assessed in a single study in twelve subjects, none of which demonstrated suppression after four weeks of treatment. However, in a separate long-term study of repeat intermittent use, a single subject manifested suppression fifty-two weeks.

Calcium metabolism was assessed in 141 subjects in a single study; 6.4% showed hypercalcemia. However, the elevations were mild (≤ 3 mmol/L, below the level at which symptoms would be expected) and resolved following discontinuation of therapy (although this was not always assessed). Additionally, the rates of hypercalcemia were similar across all arms (Dovobet, calcipotriene, betamethasone, and vehicle), and mean albumin corrected calcium values were similar across all arms at end of treatment. Hence routine laboratory monitoring of serum calcium does not appear necessary with labeled use.

Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

Chemistry, Manufacturing and Control

The applicant proposed 15, 30, 60, and — gram tube sizes. Because treatment will be restricted to 100gms per week, the — gram tube size is not acceptable. The applicant agreed and plans to submit labeling supplement for — gram tube..

Post-marketing Commitments

Four nonclinical postmarketing studies have been recommended by Dr. Norman See:

1. Evaluation of the carcinogenicity of calcipotriene (this matter is currently being evaluated by the sponsor as a post-approval commitment to NDA 20-273).
2. Evaluation of the carcinogenicity of betamethasone dipropionate in mice. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 21-852.
3. Evaluation of the carcinogenicity of betamethasone dipropionate in rats. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 21-852.
4. Evaluation of betamethasone dipropionate for effects upon female fertility, including prenatal and postnatal function.

Pediatric studies were waived for children ages 0 to 11 years of age and deferred for ages 12 to 17. The deferred pediatric study under PREA for the treatment of psoriasis vulgaris in pediatric patients ages 12 to 17 is considered a post-marketing commitment.

Conclusion

In a single, robust pivotal trial, and in combination with supportive and non-clinical studies, the applicant has demonstrated the safety and efficacy of Taclonex ointment applied once daily for four weeks for the treatment of psoriasis vulgaris in adults. I concur with the recommendations of the multi-disciplinary review team for approval for marketing.

Jill Lindstrom, MD

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/s/

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