



HAUTE AUTORITÉ DE SANTÉ

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## TRANSPARENCY COMMITTEE

### OPINION

9 May 2007

**DAIVOBET 50 µg/0.5mg/g, ointment**  
**60g tube (CIP: 360 826-8)**

**Applicant: LEO Pharma**

calcipotriol / betamethasone

List I

Marketing Authorisation (MA) date: 12 February 2003, amended 15 June 2006 (extension of indication)

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of the indication.

Previous indication: Initial topical treatment of plaque-type psoriasis (psoriasis vulgaris), where topical treatment is relevant.

New indication of 15 June 2006: Topical treatment of plaque-type psoriasis (psoriasis vulgaris), where topical treatment is relevant.

Health Technology Assessment Division

## 1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

### 1.1. Active ingredient

calcipotriol / betamethasone

### 1.2. Indication

#### Previous indication

Initial topical treatment of plaque-type psoriasis (psoriasis vulgaris), where topical treatment is relevant.

#### New description of the indication including the indication's extension beyond 4 weeks

Topical treatment of plaque-type psoriasis (psoriasis vulgaris), where topical treatment is relevant.

### 1.3. Dosage

DAIVOBET must be applied once a day to lesions. The recommended duration of treatment is of 4 weeks.

After this period, treatment with DAIVOBET may be repeated under medical supervision. The maximum daily dose must not exceed 15 g, while the maximum weekly dose must not exceed 100 g. Do not apply to more than 30% of the body surface area.

The use of this product in children and adolescents under 18 is not recommended.

## 2 SIMILAR MEDICINAL PRODUCTS

### 2.1. ATC Classification

D: Dermatology  
D05: Antipsoriatics  
D05A: Antipsoriatics for topical use  
D05AX: Other antipsoriatics for topical use  
D05AX52: Calcipotriol and combinations

### 2.2. Medicines in the same therapeutic category

The active ingredients in DAIVOBET are present in other medicinal products in a non-combined form.

There are no other fixed-dose combination involving several active ingredients for the topical treatment of psoriasis.

### 2.3. Medicines with a similar therapeutic aim

#### High-activity dermocorticosteroids (level II)

amcinomide:	PENTICORT (ointment and cream)
betamethasone:	BETNEVAL (ointment and cream) DIPROSONE 0.05% (ointment and cream)
desonide:	LOCATOP 0.1% (cream)
diflucortolone:	NERISONE (ointment and cream) NERISONE oily (cream)
difluprednane:	EPITOPIC (cream)
fluocinolone:	SYNALAR 0.025% (ointment and cream)

fluocinonide:	TOPSYNE APG 0.05% (ointment) TOPSYNE 0.05% (ointment) TOPSYNE 0.01% (ointment)
fluticasone:	FLIXOVATE (ointment and cream)
hydrocortisone:	EFFICORT HYDROPHILE 0.127% (cream) EFFICORT LIPOPHILE 0.127% (cream) LOCOÏD (ointment and cream)

#### Vitamin D3 analogues

calcipotriol:	DAIVONEX 50 µg/g
calcitriol:	SILKIS 3 µg/g
tacalcitol:	APSOR 4 µg/g (ointment)

#### Vitamin A derivatives (retinoid)

tazarotene:	ZORAC 0.05% and 0.1% (gel)
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### 3 ANALYSIS OF AVAILABLE DATA

#### **3.1. Efficacy and safety studies**

The laboratory provided two efficacy and safety studies to support its request.

##### 3.1.1. Use of DAIVONEX in combination with DAIVOBET following the initial treatment of psoriasis vulgaris<sup>1</sup>

This study, whose treatment regimen alternated between 5 days and 2 days is not mentioned in the SPC and was not taken into account by the Transparency Committee.

##### 3.1.2. 52-week safety study of DAIVOBET for the treatment of psoriasis vulgaris<sup>2</sup>

The objective was to evaluate the long-term safety of DAIVOBET based on different dosing regimens.

This multi-centre, randomised, double-blind study compared 3 groups of patients. All patients were initially treated with DAIVOBET for 4 weeks. Then, according to the randomisation, they received at a dosage of one application per day, when necessary, of one of the following treatments:

- DAIVOBET continuously for 48 weeks (group 1)
- DAIVONEX for 4 weeks, then DAIVOBET for 4 weeks, repeating this sequence for up to 48 weeks (group 2)
- DAIVONEX for 48 weeks (group 3)

This study was carried out on 634 adult patients, with a degree of psoriasis ranging from severe to less moderate, covering 10% to 30% of the body surface area, the trunk or limbs.

#### Results for the primary endpoints (safety)

The primary endpoints were:

- the percentage of patients with adverse effects caused by the treatment ;

<sup>1</sup> White S, Vender R, Thaçi D, et al. Use of calcipotriol cream (Daivonex®/Dovonex® cream) following acute treatment of psoriasis vulgaris with the calcipotriol/betamethasone dipropionate two-compound product (Daivobet®/Dovobet®). A randomized, parallel-group clinical trial. Am. J Clin Dermatol 2006; 7: 177-184.

<sup>2</sup> Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet®/Daivobet®/Taclonex®) in the treatment of psoriasis vulgaris. Br. J. Dermatol 2006; 154: 1155-1160

- the percentage of patients with adverse effects usually linked to topical corticoids, which it was possible to attribute to the treatment.

The percentage of patients with adverse effects caused by the treatment was 21.7% (45/212) in group 1 (DAIVOBET continuously for 52 weeks), 29.6% (63/213) in group 2 (alternating DAIVOBET for 4 weeks and DAIVONEX for 4 weeks) and 37.9% (78/209) in group 3 (DAIVOBET for 4 weeks followed by DAIVONEX 48 weeks). The comparison between the groups showed a percentage of adverse effects caused by the treatment in group 1 (DAIVOBET for 52 weeks) that was significantly lower than that in group 3 (DAIVOBET for 4 weeks followed by DAIVONEX 48 weeks) ( $p < 0.001$ ).

The most common adverse effects noted were: burns, itching and erythema.

The percentage of patients with an adverse effect usually linked to topical corticosteroids, which it was possible to attribute to the treatment was 4.8% (10/212) in group 1 (DAIVOBET continuously for 52 weeks), 2.8% (6/213) in group 2 (alternating DAIVOBET for 4 weeks and DAIVONEX for 4 weeks) and 2.9% (6/209) in group 3 (DAIVOBET for 4 weeks followed by DAIVONEX 48 weeks). No statistically significant difference was found between the three treatment groups in the risk of occurrence of adverse effects associated with long-term topical treatment with corticoids.

These effects were: cutaneous atrophy, depigmentation, folliculitis, bruising and purpura.

Comments:

The most common adverse effects (burns, itching and erythema) may also be signs of psoriasis rather than effects caused by the product. They are less severe than the local adverse effects caused by corticosteroids, which are not all reversible.

#### Results for the secondary endpoints (efficacy)

The secondary endpoints were the following:

- The percentage of visits where the result of the evaluation was judged to be satisfactory by the investigator. The effect of the treatment was evaluated using a global score assessing the severity on a 6-point scale. For the result to be considered satisfactory, the score had to be between 0 and 2.
- Global assessment of the treatment by the patient.

The median percentage of visits where the result of the assessment was considered to be satisfactory by the investigator was 84% in group 1 (DAIVOBET for 52 weeks), 75% in group 2 (alternating DAIVOBET for 4 weeks and DAIVONEX for 4 weeks) and 70% in group 3 (DAIVOBET for 4 weeks followed by DAIVONEX 48 weeks). The comparison between the groups indicated a percentage of visits where the result of the assessment was considered to be satisfactory by the investigator that was significantly higher in group 1 (DAIVOBET for 52 weeks) than in group 3 (DAIVOBET for 4 weeks followed by DAIVONEX 48 weeks) ( $p = 0.025$ ).

The comparison of the results in terms of the global assessment of the treatment by the patient does not show any statistically significant difference between the groups.

Comments: the efficacy was highlighted for one of the 2 secondary endpoints analysed (the percentage of visits where the result of the assessment was considered to be satisfactory). This endpoint does not take into account the extent of the lesions, unlike PASI, which is the usual endpoint.

### **3.2. Conclusion**

This study indicated that DAIVOBET administered when necessary for 52 weeks caused fewer adverse effects (of any kind) than treatment with DAIVOBET for 4 weeks followed by treatment with DAIVONEX according to the same procedures for 48 weeks.

The Transparency Committee notes the positive outcome observed with DAIVOBET in the safety study carried out over 52 weeks, supplied by the laboratory. However, it points out that this type of trial is not the most appropriate for demonstrating good tolerance of this medicine.

Furthermore, the assessment of the efficacy of DAIVOBET administered long term in relation to DAIVONEX is only based on the analysis of secondary endpoints.

## **4 TRANSPARENCY COMMITTEE CONCLUSIONS**

### **4.1. Actual benefit in the extension of the indication**

Psoriasis is a chronic, non-infectious, non-contagious and very often benign inflammatory dermatosis, which may have a significant psychosocial impact in some of its forms.

DAIVOBET is part of a symptomatic treatment.

With DAIVOBET the efficacy/adverse effects ratio is moderate beyond 4 weeks of treatment.

DAIVOBET is used as a first-line treatment.

Topical alternative treatments are available which do not have the adverse effects of corticosteroids.

The actual benefit of this medicinal product in the case of repeated use beyond 4 weeks of treatment and in compliance with the correct usage is substantial.

### **4.2. Improvement in actual benefit in the extension of the indication**

In a situation where treatment is extended beyond 4 weeks, DAIVOBET does not bring any improvement in actual benefit in relation to DAIVONEX.

The Committee points out that in the case of initial treatment for psoriasis limited to 4 weeks, "DAIVOBET provides a level IV (minor) improvement in actual benefit in terms of efficacy, speed of action and reduction in adverse effects in relation to the comparators used in clinical trials (calcipotriol, betamethasone and tacalcitol)".

### **4.3. Therapeutic use**

Treatments of psoriasis does not only depend on the severity and extent of the lesions, but also on functional, aesthetic, professional and personal prejudices, on the psychological impact of the disease and on the patient's desire for remission.

Generally, patients with a case of psoriasis which is very limited and/or psychologically well accepted are not systematically treated.

Current treatments do not produce a definitive cure for the disorder, but result in the temporary disappearance of the lesions, more or less completely.

Cutaneous hydration is often associated with topical treatments, which are the first-line treatment for limited, plaque-type psoriasis.

There are several classes of topical treatments: dermocorticosteroids, vitamin D3 analogues, retinoids (vitamin A derivatives) and, used to a lesser extent, coal tar and keratolytics.

As first-line therapy, topical treatments may be used on their own or in combination. In this case, DAIVOBET, in a fixed-dose combination with a dermocorticosteroid and vitamin D3 analogue, may be prescribed for the treatment of plaque-type psoriasis covering less than 30% of the body surface area. It must not be applied to the face, in skin folds or on the scalp.

The recommended duration of treatment with DAIVOBET is 4 weeks. After this period, if no bleaching occurs, acute treatment may be extended under medical supervision. If bleaching occurs, treatment with DAIVOBET will be followed on by maintenance treatment. If this fails, another form of treatment must be considered. In the case of long-term maintenance treatment, DAIVOBET is likely to produce the adverse effects from corticosteroids and there is little evidence of its efficacy.

#### **4.4. Target population**

The target population is not modified as a result of extending the duration of the treatment.

#### **4.5. Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals for the new indication and dosage of the MA.

##### **4.5.1. Packaging**

Appropriate for the prescription conditions..

##### **4.5.2. Reimbursement rate: 65%**