## SYNOPSIS

### Name of sponsor/company
Laboratoires LEO S.A.

### Location of study report in Regulatory Dossier for authorities

### Name of finished product
Daivobet/Dovobet Ointment

### Volume:

### Name of active ingredient
Calcipotriol and betamethasone dipropionate

### Page:

### Study title:
Repeat insult patch test with Daivobet/Dovobet Ointment - A study on the sensitisation potential of Daivobet/Dovobet Ointment and the Ointment Vehicle when applied on healthy skin in 200 healthy subjects.

### Protocol number:
MCB 0202 FR

### Investigator:
MD

### Study centre:
France

### Publication:
N/A

### Studied period:
- **First subject in (inclusion):** March 11th, 2003
- **First study-drug administration:** March 17th, 2003
- **Last study-drug administration:** June 16th, 2003
- **Last subject out (completion):** June 26th, 2003

### Clinical phase of development:
I

### Objectives:
The objective of this study was to determine the potential of repeated applications of Daivobet/Dovobet ointment and the ointment vehicle to induce sensitisation to the skin of healthy volunteers.

### Methods:
This was a randomised, double-blind, vehicle-controlled, with intra-individual comparison, single centre study.

Two hundred and twenty (220) subjects were included, in order to fulfill the criteria of 200 subjects to complete the study. Completers were subjects who completed the entire study or those who dropped out because of adverse events.

The duration of the study for each subject was 6 to 9 weeks, comprising of a 2 week run-in period followed by a 3-week induction phase and a 1-week challenge phase, separated by a 2-week rest phase. A completion visit was performed during the last day of assessment or within the week after. In case of serious adverse events ongoing at last visit and non-serious adverse events ongoing at the last visit which were classified as possibly/probably related to trial drug or not assessable, a follow-up visit was performed 2 weeks after the last visit. All subjects received both Daivobet/Dovobet ointment and its vehicle in a randomised manner.

According to randomisation, one test site per subject was allocated to Daivobet/Dovobet ointment containing 50 μg/g of calcipotriol (as hydrate) and 0.5 mg/g of betamethasone (as dipropionate) and one test site to the Daivobet/Dovobet ointment vehicle for the whole induction phase.

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All topical applications were performed on the skin of the back using occlusive dressings (Large Finn Chambers®). For each application 50 μl of each investigational product was delivered directly into a Finn Chamber® patch-test using a micropipette (Eppendorf®). The Finn Chamber® constitutes an isolated volume with a good occlusion: it is an aluminium scapula which is 12 mm in diameter. Finn Chambers® were stuck on SCANPOR® adhesive tape and fixed on the back.

During the induction phase, the investigational products were applied to the same designated sites on the left part of the back according to the randomisation list. During the challenge phase, investigational products were applied to 2 new sites on the right part of the back.

- Induction phase
A total of 9 applications was performed over a 21-day period, on Mondays, Wednesdays and Fridays (Days 1, 3, 5, 8, 10, 12, 15, 17, 19). Products applied on Mondays, Wednesdays and Fridays were removed on Wednesdays, Fridays and Mondays, respectively. After removal and scoring, a new application was performed.

- Rest phase
The induction phase was followed by a 2-week period during which no application was made.

- Challenge phase
The investigational products were applied on Day 36 and remained on skin for 48 hours. They were removed on Day 38 and the test sites scored. The sites were scored again on Days 39 and 40 after a further 24- and 48-hour period, respectively.

Sensitisation potential was based on an assessment using a visual scoring of the skin reaction. The first evaluations were done approximately 30 minutes after removal of the patches. In addition, in the challenge phase, clinical scoring was repeated approximately 24 and 48 hours after removal of the patches.

In case of serious adverse events ongoing at the last visit and non-serious adverse events ongoing at the last visit which were classified as possibly/probably related to trial drug or not assessable, a follow-up visit was performed after 2 weeks.

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<tbody>
<tr>
<td>Planned: 220</td>
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<td>Screened: 226</td>
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<tr>
<td>Included: 220</td>
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<tr>
<td>Completed trial: 206</td>
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<tr>
<td>In local tolerability analysis: 206</td>
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<td>In safety analysis: 220</td>
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### Diagnosis and main criteria for inclusion:

The subjects to be included in this study were to be healthy as defined by medical history and a physical examination (including blood pressure and urine pregnancy test for the women) made prior to inclusion. Subjects were to be 18 to 55 years old and willing to give written informed consent.

### Test product:

**DAIVOBET/DOVOBET OINTMENT** - Calcipotriol (50 μg/g) and betamethasone dipropionate (0.5 mg/g)

- **Manufacturer:** LEO Pharma
- **Unit dose:** 50 μl
- **Batch number / Expiry date:** 03 070 62 01 / April 2004

**Placebo:**

**DAIVOBET/DOVOBET OINTMENT VEHICLE**

- **Manufacturer:** LEO Pharma
- **Unit dose:** 50 μl
- **Batch number / Expiry date:** 03 070 63 01 / February 2005

### Dose/Regimen/Route:

**Test Product:**

- **Regimen:** Ten applications in total. During the induction phase: three applications per week for 3 weeks (6 repeated 48-hour topical applications and three 72-hour applications were performed on the same sites). During the challenge phase: one 48-hour topical application at a different site.
- **Mode/route:** Topical, occlusive

**Placebo:**

- **Regimen:** As for the Test Product
- **Mode/route:** Topical, occlusive

### Duration of treatment:

21 days plus a final 48-hour application after a rest period of 2 weeks.

### Criteria for Evaluation:

**Local tolerability:**

Visual scoring of skin reactions from 0 (no erythema) to 4 (severe erythema, oedema, vesicles or blisters).

**Safety:**

Monitoring for the occurrence of adverse events (AEs) and changes in physical examination, vital signs (blood pressure and pulse rate).
Statistical Methods:

Descriptive statistics accompany all analyses if not otherwise indicated. These statistics include n, mean, standard deviation, standard error of the mean, minimum, median and maximum for continuous parameters. Categorical and ordinal scale parameters were summarized with frequencies and treatment percentages.

The visual scoring and the sensitisation potential analysis was performed on the Per Protocol population. Visual scoring data were presented using descriptive statistics and graphically displayed. Results for sensitisation potential assessment were listed by subject and treatment. A frequency table presenting the count and frequency of subjects by category of sensitisation (negative/positive) and treatment was provided.

Proportion of each sensitisation category was presented graphically per treatment using bar charts.

Results and Conclusion:

The mean ± standard error of the mean (SEM) values of visual scoring of skin reactions after application of either Daivobet/Dovobet ointment or its vehicle were low. For the sites treated with Daivobet/Dovobet ointment, the mean score increased slightly from Day 10 to Day 22 during the induction phase while for the sites treated with the Daivobet/Dovobet ointment vehicle, the mean scores were almost unchanged from Day 3 to Day 22 as shown in the following figure:

![Graph showing visual scoring of skin reactions over time for different treatments. The x-axis represents days from Day 3 to Day 22, and the y-axis represents the score. Two lines are shown: one for Daivobet (first site) and one for Vehicle (first site). The graph shows a slight increase in score for the Daivobet group from Day 10 to Day 22, while the Vehicle group shows little change.](image-url)
Individual values of visual scoring of the site treated with Daivobet/Dovobet ointment or vehicle were for a majority of subjects equal or below 1 thus indicating no erythema or a barely perceptible erythema for most of the subjects. Only three subjects (one at the site of Daivobet/Dovobet ointment application, and two at the site of vehicle application) had a noticeable skin reaction which was assessed to be due to folliculitis. The results indicate that the investigational products have low skin irritation potential.

During the challenge phase, mean values of visual scoring were lower than the maximum values observed during the induction phase for Daivobet/Dovobet ointment while for the Daivobet/Dovobet ointment vehicle a slight increase in mean values of visual scoring was observed. Indeed, considering individual data, there were 27 subjects for Daivobet/Dovobet ointment and 41 subjects for Daivobet/Dovobet ointment vehicle who showed higher maximum scores during the challenge phase than during the induction phase. However, theses increases were small and were not considered to indicate any sensitisation.

The result of the visual scoring was confirmed by the investigator’s assessment of sensitisation potential on Day 40, which was negative for all subjects.

Overall, no sensitisation reaction was observed for any subject during the whole duration of the study including the induction phase.

One subject reported local mild adverse event (folliculitis) on the Daivobet/Dovobet ointment site, and 2 subjects reported mild folliculitis on the vehicle site. These AEs were judged probably related to the investigational drugs. In addition, 9 subjects reported systemic adverse events that were considered as not related to the study products. Overall, no clinically relevant changes in vital signs and physical examinations were seen during the study.

It can be concluded from these results that, under the conditions of the study, Daivobet/Dovobet ointment had no sensitisation potential and that repeated applications of Daivobet/Dovobet ointment were safe and well tolerated.