ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S) OF THE MEDICINAL PRODUCT(S), ROUTE(S) OF ADMINISTRATION, APPLICANT(S) MARKETING AUTHORISATION HOLDER(S) IN THE MEMBER STATES

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Belgium	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/0,5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Belgium	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/g + 0,5 mg/g, zalf	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Bulgaria	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet®	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Cyprus	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet® 50 microgram/g + 0.5 mg/g ointment	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Czech Republic	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet mast	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Denmark	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Denmark	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Estonia	LEO Pharmaceutical Products Industriparken 55 DK-2750 Ballerup Denmark	DAIVOBET	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Finland	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 mikrogram/g + 0,5 mg/g geeli	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Finland	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50/500 mikrog/g voide	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	DAIVOBET 50 microgrammes/0, 5 mg/g, gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
France	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	DAIVOBET 50 microgrammes/0, 5 mg/g, pommade	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Germany	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 Mikrogramm/g + 0,5 mg/g Gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Germany	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet® 50 Mikrogramm/g + 0,5 mg/g Salbe	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Greece	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/ 0.5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Greece	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/g + 0.5 mg/g	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Hungary	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet ointment	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Iceland	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 míkrógrömm/0,5 mg/g hlaup	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Iceland	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 míkróg/g + 0,5 mg/g smyrsli	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Ireland	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/g + 0.5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Ireland	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/g + 0.5 mg/g ointment	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Italy	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Italy	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Latvia	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet® 50 µg/g + 0,5 mg/g ziede	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Lithuania	LEO Pharmaceutical Products Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Luxembourg	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet Scalp 50 microgram/0,5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Luxembourg	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgrammes/g + 0,5 mg/g, onguent	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Malta	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet® 50 micrograms/g + 0.5 mg/g ointment	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Netherlands	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet gel 50 microgram/0,5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Netherlands	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet zalf 50 microgram/g + 0,5 mg/g	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Norway	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 mikrogram/g + 0,5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Norway	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 mikrogram/g + 0,5 mg/g salve	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Poland	LEO Pharmaceutical Products Ltd. A/S Industriparken 55 DK-2750 Ballerup Denmark	DAIVOBET	(50 µg + 0.5 mg)/g	Ointment	Cutaneous use
Portugal	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Portugal	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Romania	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	DAIVOBET® UNGUENT	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Slovenia	Pharmagan, d.o.o. Vodopivceva 9 SI-4000 Kranj Slovenia	Daivobet 50 mikrogramov/500 mikrogramov v 1g mazilo	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Spain	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 microgramos/g + 0,5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
Spain	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet 50 microgramos/g + 0,5 mg/g pomada	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
Sweden	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Gel	Cutaneous use

Member State EU/EEA	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Sweden	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Daivobet	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use
United Kingdom	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet 50 microgram/g + 0.5 mg/g gel	50 µg/g + 0.5 mg/g	Gel	Cutaneous use
United Kingdom	LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) Industriparken 55 DK-2750 Ballerup Denmark	Dovobet® 50 microgram/g + 0.5 mg/g ointment	50 µg/g + 0.5 mg/g	Ointment	Cutaneous use

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Daivobet and associated names (see Annex I)

Daivobet ointment is a combination product which contains the vitamin D analogue, calcipotriol monohydrate and betamethasone dipropionate.
Daivobet gel is a different formulation which contains the same active substances in the same concentrations as in Daivobet ointment.

The purpose of this Art 30 referral is to harmonise the SPC across EU member states for Daivobet ointment authorised via the Mutual Regognition Procedure (MRP) and the national authorisation. Furthermore, since Daivobet gel is an extension to Daivobet ointment and there were some differences in the SPCs.

DAIVOBET OINTMENT

Section 4.1 – Therapeutic Indications

The most current indication in the Member States (MSs) was *"treatment of psoriasis vulgaris"* and in other two MSs the indication was "*combined treatment of psoriasis"*.
The MAH proposed as the harmonised text to the ointment the following wording: "*Topical* treatment of *stable plaque* psoriasis vulgaris *amenable to topical therapy"*. This describes accurately the subjects included in the clinical studies submitted in support of the efficacy and safety of Daivobet ointment. These studies were MCB 9802 INT and MCB 9904 INT. In these studies subjects were required to have "psoriasis vulgaris amenable to treatment with topical medication" and subjects who required systemic antipsoriatic treatment or phototherapy were excluded. Subjects with unstable psoriasis (erythrodermic, exfoliative or pustular psoriasis) were excluded.

The CHMP endorsed these changes as they improve the definition of the target population and reflect the data offered in support of the indications. However, to comply with the latest version of the guidance on the SPC, the indication was amended to include *adults* as the intended to treat population.
In conclusion, the CHMP endorsed the following wording under this section:
Daivobet ointment SPC: *"Topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy in adults"*.
Daivobet gel SPC: *"Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris in adults"*.

Section 4.2 - Posology and method of administration

The wording in the national SPCs was largely reflected in the MRP SPC.
Three MSs SPC stated: *"there is experience with repeated courses of Daivobet up to 52 weeks"* which was supported by study MCB 0102 INT. The MAH proposed to delete this sentence but the CHMP considered useful to include the information in the harmonised SPC.

In one MSs SPC was not included the information that after a period of 4 weeks repeated treatment with Daivobet ointment can be initiated under medical supervision. The efficacy and safety of Daivobet ointment has been investigated for periods longer than 4 weeks in study MCB 0102 INT. Many patients who respond well to Daivobet ointment over the recommended 4 week treatment period still require repeated treatment for long term control of their psoriasis. In study MCB 0102 INT there was a trend towards greater efficacy and a lower incidence of adverse events reported in patients who remained on Daivobet ointment applied as required compared with patients who switched to other treatments.

The statement *"After this period repeated treatment with Daivobet ointment can be initiated under medical supervision*" was considered unclear by the CHMP as Daivobet treatment is presumably initiated by a doctor and treatment is presumably monitored. The MAH accepted the recommendation for rewording section 4.2 and the CHMP endorsed the proposed wording: "*If it is necessary to continue or restart treatment after this period, treatment should be continued after medical review and under regular medical supervision"*.

In one MSs SPC there were no recommendations regarding the maximum daily dose (15g) or the percentage of the body surface area to be treated (30%). Therefore it was proposed to add the wording "*the maximum daily dose should not exceed 15 g, and the maximum weekly dose should not exceed 100 g"* and "*the body surface area treated with calcipotriol containing products should not exceed 30%*". These restrictions were introduced to avoid excessive exposure to calcipotriol and the possibility of vitamin D related adverse events (e.g. hypercalcaemia). Vitamin D related adverse events resulting from extensive exposure to calcipotriol have been reported in a few cases in the literature.
The CHMP commented that, as suggested from the MAH's wording, a patient using the maximum daily dose of 15 g will exceed the maximum weekly dose of 100 g, reaching 105 g. The MAH answered to this comment that some patients may need a daily dose of 15 g during the first few days of treatment, but since efficacy during the first week of treatment is high it would be reasonable to expect that patients would apply less treatment by the end of the week as the psoriasis lesions decrease in size and severity. The CHMP proposed that the MAH either omits a weekly dose and endorsed the following: *"When using calcipotriol containing medicinal products, the maximum daily dose should not exceed 15 g."*

With regard to the risk of rebound effects mentioned in section 4.4, the CHMP questioned if there was any evidence that tapering the dose will reduce the chance of this happening. The risk of rebound effect has been included in the SPC based on data from post marketing use. These data do not contain any evidence that tapering the dose of Daivobet ointment will reduce the risk of rebound effects. It was therefore not possible to add additional wording to the statement in section 4.4.
The CHMP concluded that the MAH has justified not adding specific wording on rebound or on atrophy and has provided all requested information.

Information on use in children has been updated by the MAH according to the Quality Review of Documents guidance. The statement "*children and adolescents below the age of 18 years*" has been simplified to "*children below the age of 18 years*".

Section 4.3- Contraindications

The MAH proposed a wording in line with the MRP SPC that already largely reflected the wording of the national SPCs of several MSs.
In three MSs the wording regarding contraindications of corticosteroids was more general than in the MRP SPC. Therefore the MAH proposed a text more specific regarding the known cutaneous effects of betamethasone dipropionate. The CHMP agreed with the MAH proposal and with the addition of greater details regarding situations where steroids should not be used and endorsed the following: "*Due to the content of corticosteroid, Daivobet ointment is contraindicated in the following conditions: Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers, wounds, perianal and genital pruritus"*.

Since there is no documented information on safety and efficacy for Daivobet ointment about guttate, erythrodermic, exfoliative and pustular psoriasis as none about patients with severe renal insufficiency or severe hepatic disorders, the MAH proposed to contraindicate Daivobet in these cases based on their exclusion from the clinical trial programme.

The CHMP noted that the contraindications in erythrodermic, exfoliative and pustular psoriasis are based on medical risk of use in these conditions and are therefore considered to be absolute contraindications.
Regarding the contraindication for guttate psoriasis, this has been included in the SPC based on its exclusion from the clinical trial programme as well. The MAH agreed, however, that this is not an absolute contraindication and proposed to move it to section 4.4. The CHMP agreed to this proposal.
With regard to the contraindication in patients with severe renal and severe hepatic disorder, the MAH clarified that the contraindication has been included in the SPC based on its exclusion from the clinical trial programme, being not an absolute contraindication the information was removed from section 4.3 and the following was added in section 4.2: *"The safety and efficacy of Daivobet ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated".* The CHMP endorsed the MAH proposal for the harmonised wording.

In one MS SPC there was the contraindication in patients with disorders of calcium metabolism. The contraindication in patients with known disorder of calcium metabolism seemed appropriate by the CHMP that endorsed the following: *"Due to the content of calcipotriol Daivobet ointment is contra-indicated in patients with known disorders of calcium metabolism".*

Section 4.4 - Special warnings and precautions for use

The MAH proposed a harmonised text drafted accordingly to the one used in the MRP procedure with some amendments. The order of the information has been changed and reworded so that is in accordance with the information in the SPC for Daivobet gel: the word *"strong"* has been deleted from the definition of betamethasone dipropionate that is classified as a potent group III steroid.
Regarding precautions on the face and genitals the information *"Long-term treatment of these parts of the body should be avoided"* has been deleted because of the high risk local and systemic adverse reactions.

Local adverse reactions
In several MS's SPC the warning for use on the face was "*the ointment may/should/must not be used on the face region*" rather than "*to avoid application*". Furthermore in four MSs the text "*Skin of the face and genitals are very sensitive to corticosteroids. These areas should only be treated with weaker corticosteroids*" was either partly or not included in the SPC.
Due to the thin stratum corneum of the face and genitals these areas are particularly susceptible to local and systemic adverse effects of corticosteroids. The CHMP found that there was no clear statement that this product should not be used there and endorsed the following harmonised wording: "*Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas*".

Effects on calcium metabolism
In several MS's the statement *"treatment of more than 30% of the body surface should be avoided"* was not included in the SPC and the MAH proposed to include this wording under section 4.4. Considering that hypercalcaemia, resulting from extensive exposure to calcipotriol, has been reported in a few cases in the literature, the CHMP endorsed the MAH proposal and added a cross reference to section 4.2.

Concomitant skin infections
In two MS's the text "*When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if infection worsens, treatment with corticosteroids should be stopped"* was not included in the SPC. Secondary infection is a documented local adverse effect of treatment with topical corticosteroids. The CHMP accepted the inclusion of the above in the harmonised text.

Discontinuation of treatment and Long term use
In one MS there was no reference to rebound effects when discontinuing treatment with corticosteroids.

The risk of rebound is well documented and the EU guidelines on the investigation of products for use in psoriasis recommend the investigation of rebound.
In the same MS SPC there was also no mention of the increased risk of local and systemic corticosteroid undesirable effects in long term use which could lead to systemic adverse events that are as well known and documented.
The CHMP endorsed the mention of such warnings.

Unevaluated uses
In three MSs there was a warning *"due to lack of experience it is necessary to be more careful with serious liver or kidney diseases"*. The reference to patients with severe renal insufficiency or severe hepatic disorders was removed from this section and included under section 4.2

Concurrent treatment and UV exposure
The MAH proposed the deletion of *locally* from the following: "*There is no experience with concurrent use of other anti-psoriatic products administered locally* or systemically or with phototherapy".
The study MBL 0404 FR, conducted for the development of Daivobet gel, investigated the adrenal response to adrenocorticotropic hormone (ACTH) and its results were included in the approved Daivobet gel SPC. The study MBL 0404 FR investigated also the systemic effects of the combined use of Daivobet gel (used on the scalp) and Daivobet ointment (used on the body) in patients with psoriasis vulgaris on these areas. Patients with psoriasis vulgaris often have lesions on the scalp as well as the body. Other studies were submitted in support of the efficacy and safety of Daivobet ointment on the body (MCB 9802 INT and MCB 9904 INT), patients in these studies were allowed to use other topical medication on scalp psoriasis. The MAH proposed to add some detailed information from these mentioned studies in the harmonized SPC.
The CHMP considered acceptable that in the studies performed to support the gel and ointment formulations, concomitant medication to treat psoriasis of the body and scalp respectively was permitted. When the gel and scalp psoriasis were assessed, other treatments were permitted for body psoriasis. When the ointment and body were assessed, other treatments were allowed for face and scalp.
It did appear that there was no experience of combination use of Daivobet and other topical treatments at the same site therefore the CHMP endorsed the following sentence*:" There is no experience for the use of this medicinal product on the scalp. Daivobet ointment for body psoriasis lesions has been used in combination with Daivobet gel for scalp psoriasis lesions, but there is no experience of combination of Daivobet with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy"*.

In one MS, the text "*During Daivobet ointment treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UVR only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3)*" was not included in the SPC. This recommendation is based on non-clinical photo(co)carcinogenicity data. Based on post marketing data, standard use of calcipotriol followed by average and standard UV-exposure does not seem to imply any special risk for patients using calcipotriol.
The CHMP believed relevant and adequate this recommendation for the harmonised SPC.

Section 4.6 - Pregnancy and lactation

The wording in the national SPC of a number of MSs largely reflected the wording used in MRP SPC. The CHMP endorsed the harmonised text under this section.

Section 4.8 - Undesirable effects

The MAH proposed a harmonised text drafted accordingly to the one used in the MRP procedure with some amendments.

The CHMP agreed to the MAH proposal regarding the addition of *Rebound effect* as stated in section 4.4. and endorsed following: "*Rebound effect after end of treatment has been reported but the frequency of this is not known".*

The text "*impact on the metabolic control of diabetes mellitus"* has also been agreed by the CHMP as undesirable effects of betamethasone dipropionate accordingly to the cross reference from section 4.4.

In one SPC the undesirable effects were not tabulated by MedDRA SOC (System Organ Class) as recommended in the EU SPC guideline. Finally, the possibility of more frequent systemic effects "*under occlusion*" was not mentioned. "*Penetration through the stratum corneum is enhanced under occlusion"* was also added in order to make clinician aware of this possibility.
One SPC did not include: "*Based on data from clinical trials and post market use the common undesirable effects are pruritus, rash and burning sensation of skin. Uncommon undesirable effects are skin pain or irritation, dermatitis, erythema, exacerbation of psoriasis, folliculitis and application site pigmentation changes. Pustular psoriasis is a rare undesirable effect*". The MAH believed that the addition of this information would give the clinician a useful short summary of the derivation of the data in this section and the more uncommon undesirable effects of Daivobet ointment.
The CHMP noted that the changes proposed by the MAH reflect the current safety experience.

Section 4.9 – Overdose

The wording in the national SPC of a number of MSs largely reflected the wording used in MRP.
In two MSs the SPC did not include the information on the spontaneous report of overdose of Daivobet ointment. The MAH believed useful the insertion of the following: "*It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Daivobet ointment weekly (corresponding to a daily dose of approximately 34 g) for 5 months (maximum recommended dose 15 g daily) developed Cushing's syndrome and pustular psoriasis after abruptly stopping treatment".*

The CHMP considered the addition of the information on misuse of Daivobet helpful and appropriate and other changes were considered acceptable.

Section 5.1 - Pharmacodynamic properties

Calcipotriol is a vitamin D analogue. In vitro data suggests that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.

The wording in the national SPCs of a number of MSs largely reflected the wording in MRP SPC.
In some MSs betamethasone dipropionate was described as a *"glucocorticoid showing the general characteristics of the corticosteroids".* This description is more general than in the MRP SPC: *"Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties, however, without curing the underlying condition"*. Adoption of the proposed text would give clinicians extra useful information regarding the specific actions of the corticosteroid component of Daivobet ointment. The pharmaco-therapeutic group *"Like other topical corticosteroids"* has also been added. This is in accordance with the DCP approved Daivobet gel SPC.

The CHMP asked the MAH to clarify the adverse events of concern possibly related to long term corticoid use. The MAH proposed the following amendment in section 5.1: "*A safety study in 634 psoriasis patients has investigated repeated courses of Daivobet ointment used once daily as required, either alone or alternating with Daivonex for up to 52 weeks, compared with Daivonex used alone for 48 weeks after an initial course of Daivobet ointment. Adverse drug reactions were reported by 21.7 % of the patients in the Daivobet ointment group, 29.6 % in the Daivobet ointment /Daivonex*

alternating group and 37.9 % in the Daivonex group. The adverse drug reactions that were reported by more than 2 % of the patients in the Daivobet ointment group were pruritus (5.8 %) and psoriasis (5.3 %). Adverse events of concern possibly related to long-term corticosteroid use (e.g. skin atrophy, folliculitis, depigmentation, furuncle and purpura) were reported by 4.8 % of the patients in the Daivobet ointment group, 2.8 % in the Daivobet ointment /Daivonex alternating group and 2.9 % in the Daivonex group."

As outlined in section 4.4, information about results from a clinical study, MBL 0404 FR, where adrenal response to adrenocorticotropic hormone (ACTH) was determined, has been included.
To improve clarity the CHMP endorsed the following: "*Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis, using up to 106 g per week combined Daivobet gel and Daivobet ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6 %) after 4 weeks of treatment and in 2 of 11 patients (18.2 %) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients. With regards to HPA suppression, therefore, this study shows some evidence that very high doses of Daivobet gel and ointment may have a weak effect on the HPA axis.*"

Section 5.2 - Pharmacokinetic properties

Proposed text: *Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet ointment formulation is less than 1% of the dose (2.5 g) when applied to normal skin (625 cm²) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids.*

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

This proposed text is identical to the current MRP SPC except for the following:
As outlined in section 4.4, information about the pharmacokinetic results from a clinical study, MBL 0404 FR has been included as follows: "*Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients treated for 4 or 8 weeks with both Daivobet gel and Daivobet ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients."*

The wording in the national SPCs of several MS largely was reflected in MRP SPC.
In three MS the SPC was more general and did not include any study results. The text proposed by the MAH gave the clinician more specific information on the available pharmacokinetic data.

One SPC did not include information about the possibility of increased absorption of topical steroids under occlusive dressings. Penetration through the stratum corneum is enhanced under occlusion thus the addition of this information would make the clinician aware of this possibility.

The CHMP found the MAH's proposal appropriate and acceptable and endorsed the harmonised wording under this section.

Section 5.3 - Preclinical safety data

The harmonised text proposed by the MAH was in line to the MRP SPC. However, in a number of member states alternative text has been included following the outcome of National Procedures. This text was originally proposed by the MAH as part of a type II variation to update the SPC following the results of two non-clinical studies, a carcinogenicity study and a photo(co)carcinogenicity study.

The CHMP noted that, according to the Guideline on Summary of Product Characteristics, the findings of the non-clinical testing, the carcinogenicity study and the photo(co)carcinogenicity study, should be described in brief and qualitative statements.
The MAH replied that they would prefer to keep the detailed description of the tests because their result indicates a reduction in the time required for UVR to induce the formation of skin tumours in male mice. Comparable adverse reactions were not observed in clinical studies.
The information was therefore considered of relevance to the prescriber in recognising the safety profile of Daivobet ointment and in supporting precautionary measures that are included in other relevant sections of the SPC as Section 4.4.
The CHMP did not consider necessary to provide the detail of the photocarcinogenicity study and endorsed the following: *"Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours".*

DAIVOBET GEL

No major updates to the Daivobet gel SPC according to the adoption of Daivobet ointment SPC (MRP) were required.

Section 4.8 - Undesirable effects

The MAH proposed a harmonised text in line to the DCP SPC with some amendments. The text "*impact on the metabolic control of diabetes mellitus"* has been added to the undesirable effects of betamethasone dipropionate as already stated in section 4.4 of the DCP SPC.
The CHMP found the changes proposed appropriate and acceptable.

Quality Module

The quality module for Daivobet ointment has also been assessed and its harmonisation has been agreed by the CHMP. The harmonisation of the quality module was requested by the MAH at the beginning of this Referral procedure.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holders have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Daivobet and associated names (see Annex I).

ANNEX III

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

Note: This SPC, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the Member State Competent Authorities, in liaison with the Reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Daivobet and associated names (see Annex I) 50 micrograms/0.5 mg/g ointment
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of ointment contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ointment.
Off-white to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of stable plaque psoriasis vulgaris amenable to topical therapy in adults.

4.2 Posology and method of administration

Posology
Daivobet ointment should be applied to the affected area once daily. The recommended treatment period is 4 weeks. There is experience with repeated courses of Daivobet up to 52 weeks. If it is necessary to continue or restart treatment after 4 weeks, treatment should be continued after medical review and under regular medical supervision.

When using calcipotriol containing medicinal products, the maximum daily dose should not exceed 15 g. The body surface area treated with calcipotriol containing medicinal products should not exceed 30 % (see section 4.4).

Special populations
Renal and hepatic impairment
The safety and efficacy of Daivobet ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Daivobet ointment in children below 18 years have not been established. No data are available.

Method of administration
Daivobet ointment should be applied to the affected area. In order to achieve optimal effect, it is not recommended to take a shower or bath immediately after application of Daivobet ointment.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Daivobet ointment is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Due to the content of calcipotriol Daivobet ointment is contra-indicated in patients with known disorders of calcium metabolism.
Due to the content of corticosteroid Daivobet ointment is contraindicated in the following conditions: Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers, wounds, perianal and genital pruritus.

4.4 Special warnings and precautions for use

Effects on endocrine system
Daivobet ointment contains a potent group III steroid and concurrent treatment with other steroids must be avoided. Adverse reactions found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus may occur also during topical corticosteroid treatment due to systemic absorption. Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. Application on large areas of damaged skin or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of corticosteroids (see section 4.8).

In a study in patients with both extensive scalp and extensive body psoriasis using a combination of high doses of Daivobet gel (scalp application) and high doses of Daivobet ointment (body application), 5 of 32 patients showed a borderline decrease in cortisol response to adrenocorticotropic hormone (ACTH) challenge after 4 weeks of treatment (see section 5.1).

Effects on calcium metabolism
Due to the content of calcipotriol, hypercalcaemia may occur if the maximum daily dose (15 g) is exceeded. Serum calcium is, however, quickly normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are followed. Treatment of more than 30 % of the body surface should be avoided (see section 4.2).

Local adverse reactions
Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas. The patient must be instructed in correct use of the medicinal product to avoid application and accidental transfer to the face, mouth and eyes. Hands must be washed after each application to avoid accidental transfer to these areas.

Concomitant skin infections
When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if infection worsens, treatment with corticosteroids should be stopped.

Discontinuation of treatment
When treating psoriasis with topical corticosteroids there may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

Long-term use
With long-term use there is an increased risk of local and systemic corticosteroid adverse reactions. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated uses
There is no experience for the use of Daivobet ointment in guttate psoriasis.

Concurrent treatment and UV exposure
There is no experience for the use of this medicinal product on the scalp. Daivobet ointment for body psoriasis lesions has been used in combination with Daivobet gel for scalp psoriasis lesions, but there is no experience of combination of Daivobet with other topical anti-psoriatic products at the same treatment arrea, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During Daivobet ointment treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UVR only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Daivobet ointment in pregnant women. Studies in animals with glucocorticoids have shown reproductive toxicity (see section 5.3), but a number of epidemiological studies have not revealed congenital anomalies among infants born to women treated with corticosteroids during pregnancy. The potential risk for humans is uncertain. Therefore, during pregnancy, Daivobet ointment should only be used when the potential benefit justifies the potential risk.

Breastfeeding
Betamethasone passes into breast milk but risk of an adverse effect on the infant seems unlikely with therapeutic doses. There are no data on the excretion of calcipotriol in breast milk. Caution should be exercised when prescribing Daivobet ointment to women who breast feed. The patient should be instructed not to use Daivobet ointment on the breast when breast feeding.

Fertility
Studies in rats with oral doses of calcipotriol or betamethasone dipropionate demonstrated no impairment of male and female fertility.

4.7 Effects on ability to drive and use machines

Daivobet has no or negligible influence on the ability to drive and to use machines.

4.8 Undesirable effects

The trial programme for Daivobet ointment has so far included more than 2,500 patients and has shown that approximately 10 % of patients can be expected to experience a non-serious undesirable effect.
These reactions are usually mild and cover mainly various skin reactions like rash, pruritus and burning sensation. Pustular psoriasis has been reported rarely. Rebound effect after end of treatment has been reported but the frequency of this is not known.

Based on data from clinical trials and postmarket use the following adverse reactions are listed for Daivobet ointment.
The adverse reactions are listed by MedDRA System Organ Class, and the individual adverse reactions are listed starting with the most frequently reported. Within each frequency grouping, the adverse reactions are listed in order of decreasing seriousness.
The following terminologies have been used in order to classify the frequencies of adverse reactions:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

Skin and subcutaneous tissue disorders	
Common	Pruritus Rash Burning sensation of skin
Uncommon	Exacerbation of psoriasis Skin pain or irritation Dermatitis Erythema Folliculitis Application site pigmentation changes
Rare	Pustular psoriasis
General disorders and administration site conditions	
Not known	Rebound effect - included in section 4.4

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone, respectively:

Calcipotriol
Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, psoriasis aggravated, photosensitivity and hypersensitivity reactions including very rare cases of angioedema and facial oedema.
Systemic effects after topical use may appear very rarely causing hypercalcaemia or hypercalciuria (see section 4.4).

Betamethasone (as dipropionate)
Local reactions can occur after topical use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When treating psoriasis there may be a risk of generalised pustular psoriasis.
Systemic reactions due to topical use of corticosteroids are rare in adults, however they can be severe. Adrenocortical suppression, cataract, infections, impact on the metabolic control of diabetes mellitus and increase of intra-ocular pressure can occur, especially after long term treatment. Systemic reactions occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long term treatment (see section 4.4).

4.9 Overdose

Use above the recommended dose may cause elevated serum calcium which should rapidly subside when treatment is discontinued.
Excessive prolonged use of topical corticosteroids may suppress the pituitary-adrenal functions resulting in secondary adrenal insufficiency which is usually reversible. In such cases symptomatic treatment is indicated.
In case of chronic toxicity the corticosteroid treatment must be discontinued gradually.

It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Daivobet ointment weekly (corresponding to a daily dose of approximately 34 g) for 5 months (maximum recommended dose 15 g daily) developed Cushing's syndrome and pustular psoriasis after abruptly stopping treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics. Other antipsoriatics for topical use, Calcipotriol, combinations. ATC Code: D05AX52

Calcipotriol is a vitamin D analogue. In vitro data suggests that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.

Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppresive properties, however, without curing the underlying condition. Through occlusion the effect can be enhanced due to increased penetration of the stratum corneum. The incidence of adverse events will increase because of this. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

A safety study in 634 psoriasis patients has investigated repeated courses of Daivobet ointment used once daily as required, either alone or alternating with Daivonex, for up to 52 weeks, compared with Daivonex used alone for 48 weeks after an initial course of Daivobet ointment. Adverse drug reactions were reported by 21.7 % of the patients in the Daivobet ointment group, 29.6 % in the Daivobet ointment/Daivonex alternating group and 37.9 % in the Daivonex group. The adverse drug reactions that were reported by more than 2 % of the patients in the Daivobet ointment group were pruritus (5.8 %) and psoriasis (5.3 %). Adverse events of concern possibly related to long-term corticosteroid use (e.g. skin atrophy, folliculitis, depigmentation, furuncle and purpura) were reported by 4.8 % of the patients in the Daivobet ointment group, 2.8 % in the Daivobet ointment/Daivonex alternating group and 2.9 % in the Daivonex group.

Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis, using up to 106 g per week combined Daivobet gel and Daivobet ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6 %) after 4 weeks of treatment and in 2 of 11 patients (18.2 %) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients. With regard to HPA suppression, therefore, this study shows some evidence that very high doses of Daivobet gel and ointment may have a weak effect on the HPA axis.

5.2 Pharmacokinetic properties

Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet ointment is less than 1 % of the dose (2.5 g) when applied to normal skin (625 cm^2) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Absorption through damaged skin is approx. 24 %.

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. Protein binding is approx. 64 %. Plasma elimination half-life after intravenous application is 5-6 hours. Due to the formation of a depot in the skin elimination after dermal application is in order of days. Betamethasone is metabolised especially in the liver, but also in the kidneys to glucuronide and sulphate esters. The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). In rats, tissue

distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients treated for 4 or 8 weeks with both Daivobet gel and Daivobet ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients.

5.3 Preclinical safety data

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction toxicity studies with long-term oral administration of corticosteroids to rats, prolonged gestation and prolonged and difficult labour were detected. Moreover, reduction in offspring survival, body weight and body weight gain was observed. There was no impairment of fertility. The relevance for humans is unknown.

A dermal carcinogenicity study with calcipotriol in mice revealed no special hazard to humans.

Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.

No carcinogenicity or photocarcinogenicity studies have been performed with betamethasone dipropionate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid paraffin
Polyoxypropylene-15 stearyl ether
All-rac-α-tocopherol
White soft paraffin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening: 1 year.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Aluminium/epoxyphenol tubes with polyethylene screw cap.
Tube sizes: 3 (sample), 15, 30, 60, 100 and 120 g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of: {name of MS/Agency}

1. NAME OF THE MEDICINAL PRODUCT

Daivobet and associated names (see Annex I) 50 micrograms/0.5 mg/g gel
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

Excipient: 160 micrograms butylated hydroxytoluene/g gel

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gel.
An almost clear, colourless to slightly off-white gel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate "non-scalp" plaque psoriasis vulgaris in adults.

4.2 Posology and method of administration

Posology
Daivobet gel should be applied to affected areas once daily. The recommended treatment period is 4 weeks for scalp areas and 8 weeks for "non-scalp" areas. If it is necessary to continue or restart treatment after this period, treatment should be continued after medical review and under regular medical supervision.

When using calcipotriol containing medicinal products, the maximum daily dose should not exceed 15 g. The body surface area treated with calcipotriol containing medicinal products should not exceed 30 % (see section 4.4).

If used on the scalp
All the affected scalp areas may be treated with Daivobet gel. Usually an amount between 1 g and 4 g per day is sufficient for treatment of the scalp (4 g corresponds to one teaspoon).

Special populations
Renal and hepatic impairment
The safety and efficacy of Daivobet gel in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Daivobet gel in children below 18 years have not been established. No data are available.

Method of administration

The bottle should be shaken before use and Daivobet gel applied to the affected area. Daivobet gel should not be applied directly to the face or eyes. The hands should be washed after use. In order to achieve optimal effect, it is not recommended to take a shower or bath, or to wash the hair in case of scalp application, immediately after application of Daivobet gel. Daivobet gel should remain on the skin during the night or during the day.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Daivobet gel is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Due to the content of calcipotriol, Daivobet gel is contraindicated in patients with known disorders of calcium metabolism.
Due to the content of corticosteroid, Daivobet gel is contraindicated in the following conditions: Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers, wounds, perianal and genital pruritus.

4.4 Special warnings and precautions for use

Effects on endocrine system
Daivobet gel contains a potent group III steroid and concurrent treatment with other steroids must be avoided. Adverse reactions found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus, may occur also during topical corticosteroid treatment due to systemic absorption. Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. Application on large areas of damaged skin or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of corticosteroids (see section 4.8).

In a study in patients with both extensive scalp and extensive body psoriasis using a combination of high doses of Daivobet gel (scalp application) and high doses of Daivobet ointment (body application), 5 of 32 patients showed a borderline decrease in cortisol response to adrenocorticotropic hormone (ACTH) challenge after 4 weeks of treatment (see section 5.1).

Effects on calcium metabolism
Due to the content of calcipotriol, hypercalcaemia may occur if the maximum daily dose (15 g) is exceeded. Serum calcium is, however, quickly normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are followed. Treatment of more than 30 % of the body surface should be avoided (see section 4.2).

Local adverse reactions
Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas. Uncommon local adverse reactions (such as eye irritation or irritation of facial skin) were observed, when the medicinal product was accidentally administered in the area of face, or accidentally to the eyes or conjunctives (see sections 4.8 and 5.1). The patient must be instructed in correct use of the medicinal product to avoid application and accidental transfer to the face, mouth and eyes. Hands must be washed after each application to avoid accidental transfer to these areas.

Concomitant skin infections
When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if infection worsens, treatment with corticosteroids should be stopped.

Discontinuation of treatment

When treating psoriasis with topical corticosteroids, there may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

Long-term use
With long-term use there is an increased risk of local and systemic corticosteroid adverse reactions. The treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated uses
There is no experience for the use of Daivobet gel in guttate psoriasis.

Concurrent treatment and UV exposure
Daivobet ointment for body psoriasis lesions has been used in combination with Daivobet gel for scalp psoriasis lesions, but there is no experience of combination of Daivobet with other topical anti-psoriatic products at the same treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.

During Daivobet gel treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with UVR only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3).

Adverse reactions to excipients
Daivobet gel contains butylated hydroxytoluene (E321), which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Daivobet gel in pregnant women. Studies in animals with glucocorticoids have shown reproductive toxicity (see section 5.3), but a number of epidemiological studies have not revealed congenital anomalies among infants born to women treated with corticosteroids during pregnancy. The potential risk for humans is uncertain. Therefore, during pregnancy, Daivobet gel should only be used when the potential benefit justifies the potential risk.

Breastfeeding
Betamethasone passes into breast milk, but risk of an adverse effect on the infant seems unlikely with therapeutic doses. There are no data on the excretion of calcipotriol in breast milk. Caution should be exercised when prescribing Daivobet gel to women who breast-feed. The patient should be instructed not to use Daivobet on the breast when breast-feeding.

Fertility
Studies in rats with oral doses of calcipotriol or betamethasone dipropionate demonstrated no impairment of male and female fertility.

4.7 Effects on ability to drive and use machines

Daivobet gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The clinical trial programme for Daivobet gel has so far included more than 4,700 patients of whom more than 2,100 were treated with Daivobet gel. Approximately 8 % of patients treated with Daivobet gel experienced a non-serious adverse reaction.
These reactions are usually mild and cover mainly various skin reactions with pruritus being the most common.

Based on data from clinical trials and postmarket use the following adverse reactions are listed for Daivobet gel.
The adverse reactions are listed by MedDRA System Organ Class, and the individual adverse reactions are listed starting with the most frequently reported. Within each frequency grouping, the adverse reactions are listed in order of decreasing seriousness.
The following terminologies have been used in order to classify the frequencies of adverse reactions:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

Eye disorders	
Uncommon	Eye irritation
Skin and subcutaneous tissue disorders	
Common	Pruritus
Uncommon	Exacerbation of psoriasis Burning sensation of skin Skin pain or irritation Folliculitis Dermatitis Erythema Acne Dry skin Rash Pustular rash

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone, respectively:

Calcipotriol
Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, psoriasis aggravated, photosensitivity and hypersensitivity reactions including very rare cases of angioedema and facial oedema.
Systemic effects after topical use may appear very rarely causing hypercalcaemia or hypercalciuria (see section 4.4).

Betamethasone (as dipropionate)
Local reactions can occur after topical use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When treating psoriasis there may be a risk of generalised pustular psoriasis.

Systemic reactions due to topical use of corticosteroids are rare in adults, however they can be severe. Adrenocortical suppression, cataract, infections, impact on the metabolic control of diabetes mellitus and increase of intra-ocular pressure can occur, especially after long term treatment. Systemic reactions occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long term treatment (see section 4.4).

4.9 Overdose

Use above the recommended dose may cause elevated serum calcium which should rapidly subside when treatment is discontinued.
Excessive prolonged use of topical corticosteroids may suppress the pituitary-adrenal functions, resulting in secondary adrenal insufficiency which is usually reversible. In such cases, symptomatic treatment is indicated.
In case of chronic toxicity, the corticosteroid treatment must be discontinued gradually.

It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Daivobet ointment weekly (corresponding to a daily dose of approximately 34 g) for 5 months (maximum recommended dose 15 g daily) developed Cushing's syndrome and pustular psoriasis after abruptly stopping treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics. Other antipsoriatics for topical use, Calcipotriol, combinations. ATC Code: D05AX52

Calcipotriol is a vitamin D analogue. In vitro data suggest that calcipotriol induces differentiation and suppresses proliferation of keratinocytes. This is the proposed basis for its effect in psoriasis.

Like other topical corticosteroids, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppresive properties, however, without curing the underlying condition. Through occlusion the effect can be enhanced due to increased penetration of the stratum corneum. The incidence of adverse events will increase because of this. In general, the mechanism of the anti-inflammatory activity of the topical steroids is unclear.

Adrenal response to ACTH was determined by measuring serum cortisol levels in patients with both extensive scalp and body psoriasis, using up to 106 g per week combined Daivobet gel and Daivobet ointment. A borderline decrease in cortisol response at 30 minutes post ACTH challenge was seen in 5 of 32 patients (15.6 %) after 4 weeks of treatment and in 2 of 11 patients (18.2 %) who continued treatment until 8 weeks. In all cases, the serum cortisol levels were normal at 60 minutes post ACTH challenge. There was no evidence of change of calcium metabolism observed in these patients. With regard to HPA suppression, therefore, this study shows some evidence that very high doses of Daivobet gel and ointment may have a weak effect on the HPA axis.

The efficacy of once daily use of Daivobet gel was investigated in two randomised, double-blind, 8-week clinical studies including a total of more than 2,900 patients with scalp psoriasis of at least mild severity according to the Investigator's Global Assessment of disease severity (IGA). Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and (in one of the studies) the gel vehicle alone, all used once daily. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that Daivobet gel was statistically significantly more effective than the comparators. Results for speed of onset based on similar data at week 2 also showed Daivobet gel to be statistically significantly more effective than the comparators.

% of patients with absent or very mild disease	Daivobet gel (n=1,108)	Betamethasone dipropionate (n=1,118)	Calcipotriol (n=558)	Gel vehicle (n=136)
week 2	53.2 %	42.8 %[1]	17.2 %[1]	11.8 %[1]
week 8	69.8 %	62.5 %[1]	40.1 %[1]	22.8 %[1]

[1] Statistically significantly less effective than Daivobet gel (P<0.001)

The efficacy of once daily use of Daivobet gel on non-scalp regions of the body was investigated in a randomised, double-blind, 8-week clinical study including 296 patients with psoriasis vulgaris of mild or moderate severity according to the IGA. Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone, all used once daily. Primary response criteria were controlled disease according to the IGA at week 4 and week 8. Controlled disease was defined as 'clear' or 'minimal disease' for patients with moderate disease at baseline or 'clear' for patients with mild disease at baseline. The percentage change in Psoriasis Severity and Area index (PASI) from baseline to week 4 and week 8 were secondary response criteria.

% of patients with controlled disease	Daivobet gel (n=126)	Betamethasone dipropionate (n=68)	Calcipotriol (n=67)	Gel vehicle (n=35)
week 4	20.6 %	10.3 %[1]	4.5 %[1]	2.9 %[1]
week 8	31.7 %	19.1 %[1]	13.4 %[1]	0.0 %[1]

[1] Statistically significantly less effective than Daivobet gel (P<0.05)

Mean percentage reduction in PASI (SD)	Daivobet gel (n=126)	Betamethasone dipropionate (n=68)	Calcipotriol (n=67)	Gel vehicle (n=35)
week 4	50.2 (32.7)	40.8 (33.3)[1]	32.1 (23.6)[1]	17.0 (31.8)[1]
week 8	58.8 (32.4)	51.8 (35.0)	40.8 (31.9)[1]	11.1 (29.5)[1]

[1] Statistically significantly less effective than Daivobet gel (P<0.05)

Another randomised, investigator-blinded clinical study including 312 patients with scalp psoriasis of at least moderate severity according to the IGA investigated use of Daivobet gel once daily compared with Daivonex Scalp solution twice daily for up to 8 weeks. Results for the primary response criterion (absent or very mild disease according to the IGA at week 8) showed that Daivobet gel was statistically significantly more effective than Daivonex Scalp solution.

% of patients with absent or very mild disease	Daivobet gel (n=207)	Daivonex Scalp solution (n=105)
week 8	68.6 %	31.4 %[1]

[1] Statistically significantly less effective than Daivobet gel (P<0.001)

A randomised, double-blind long-term clinical study including 873 patients with scalp psoriasis of at least moderate severity (according to the IGA) investigated the use of Daivobet gel compared with calcipotriol in the gel vehicle. Both treatments were applied once daily, intermittently as required, for up to 52 weeks. Adverse events possibly related to long-term use of corticosteroids on the scalp, were identified by an independent, blinded panel of dermatologists. There was no difference in the percentages of patients experiencing such adverse events between the treatment groups (2.6 % in the Daivobet gel group and 3.0 % in the calcipotriol group; P=0.73). No cases of skin atrophy were reported.

5.2 Pharmacokinetic properties

The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Daivobet gel is comparable to Daivobet ointment in rats and minipigs. Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Daivobet ointment formulation is less than 1 % of the dose (2.5 g) when applied to normal skin (625 cm^2) for 12 hours. Application to psoriasis plaques and under occlusive dressings may increase the absorption of topical corticosteroids. Absorption through damaged skin is approx. 24 %.

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. Protein binding is approx. 64 %. Plasma elimination half-life after intravenous application is 5-6 hours. Due to the formation of a depot in the skin elimination after dermal application is in order of days. Betamethasone is metabolised especially in the liver, but also in the kidneys to glucuronide and sulphate esters. The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

Calcipotriol and betamethasone dipropionate were below the lower limit of quantification in all blood samples of 34 patients treated for 4 or 8 weeks with both Daivobet gel and Daivobet ointment for extensive psoriasis involving the body and scalp. One metabolite of calcipotriol and one metabolite of betamethasone dipropionate were quantifiable in some of the patients.

5.3 Preclinical safety data

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction toxicity studies with long-term oral administration of corticosteroids to rats, prolonged gestation and prolonged and difficult labour were detected. Moreover, reduction in offspring survival, body weight and body weight gain was observed. There was no impairment of fertility. The relevance for humans is unknown.

A dermal carcinogenicity study with calcipotriol in mice revealed no special hazard to humans.

Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.

No carcinogenicity or photocarcinogenicity studies have been performed with betamethasone dipropionate.

In local tolerability studies in rabbits, Daivobet gel caused mild to moderate skin irritation and a slight transient irritation of the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, liquid
Polyoxypropylene-15 stearyl ether
Castor oil, hydrogenated
Butylhydroxytoluene (E321)
All-rac-α-tocopherol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After first opening: 3 months.

6.4 Special precautions for storage

Do not refrigerate. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

High-density polyethylene bottles with low-density polyethylene nozzle and a high-density polyethylene screw cap. The bottles are placed in cartons.
Pack sizes: 15, 30, 60 and 2 x 60 g.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of: {name of MS/Agency}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Daivobet ointment in tubes of 15 g, 30 g, 60 g, 100 g or 120 g

The text for the outer packaging (carton) and immediate packaging (tube) is the same, except where it is indicated to apply for carton or tube, respectively.

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Daivobet and associated names (see Annex I) 50 micrograms/0.5 mg/g ointment
[See Annex I - To be completed nationally]
Calcipotriol/betamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of ointment contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

3. LIST OF EXCIPIENTS

Other ingredients:
Liquid paraffin, all-rac-α-tocopherol, polyoxypropylene-15 stearyl ether, white soft paraffin

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

Pack sizes:
15 g
30 g
60 g
100 g
120 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Cutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Carton: Shelf life after first opening: 1 year

Carton: Date opened: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Carton for 15 g, 30 g, 60 g, 100 g or 120 g pack sizes:
[To be completed nationally]
Daivobet 50 micrograms/0.5 mg/g ointment

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Daivobet ointment in tubes of 3 g

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Daivobet and associated names (see Annex I) 50 micrograms/0.5 mg/g ointment
[See Annex I - To be completed nationally]
Calcipotriol/betamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of ointment contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

3. LIST OF EXCIPIENTS

Other ingredients:
Liquid paraffin, all-rac-α-tocopherol, polyoxypropylene-15 stearyl ether, white soft paraffin

4. PHARMACEUTICAL FORM AND CONTENTS

Ointment

Pack sizes:
3 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Cutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Shelf life after first opening: 1 year

Date opened: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Carton for 3 g pack size:
[To be completed nationally]
Daivobet ointment

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS, TUBE

Daivobet ointment in tubes of 3 g

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

[To be completed nationally]
Daivobet and associated names (see Annex I) 50 micrograms/0.5 mg/g ointment
[See Annex I - To be completed nationally]
Calcipotriol/betamethasone

Cutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Daivobet gel in bottles of 15 g, 30 g and 60 g

The text for the outer packaging (carton) and immediate packaging (bottle) is the same, except where it is indicated to apply for carton or bottle, respectively.

1. NAME OF THE MEDICINAL PRODUCT

[To be completed nationally]
Daivobet and associated names (see Annex I) 50 micrograms/0.5 mg/g gel
[See Annex I - To be completed nationally]
calcipotriol/betamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One gram of gel contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

3. LIST OF EXCIPIENTS

Other ingredients:
Paraffin, liquid, polyoxypropylene-15 stearyl ether, hydrogenated castor oil, butylhydroxytoluene (E321), all-rac-α-tocopherol.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Gel

Bottle text:
15 g
30 g
60 g

Carton text:
15 g
30 g
60 g
2 x 60 g (valid for the packaging containing two 60 g bottles)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Shake the bottle before use.
Do not apply directly to the face or eyes.
Wash hands after use.
Read the package leaflet before use.

Cutaneous use.
For external use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Bottle text: Lot/EXP – see the bottom of the bottle.
After first opening: 3 months.

Carton text: Lot/EXP – see the bottom of the carton.
After first opening: 3 months.

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate. Keep the bottle in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Bottle text: Lot/EXP – see the bottom of the bottle.
-
Carton text: Lot/EXP – see the bottom of the carton.

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]
Carton text: Daivobet gel.

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Daivobet and associated names (see Annex I) **50 micrograms/0.5 mg/g ointment**
[See Annex I - To be completed nationally]
calcipotriol/betamethasone

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT DAIVOBET IS AND WHAT IT IS USED FOR

Daivobet ointment is used on the skin to treat plaque psoriasis (psoriasis vulgaris) in adults. Psoriasis is caused by your skin cells being produced too quickly. This causes redness, scaling and thickness of your skin.

Daivobet ointment contains calcipotriol and betamethasone. Calcipotriol helps to bring the rate of skin cell growth back to normal and betamethasone acts to reduce inflammation.

2. BEFORE YOU USE DAIVOBET

Do not use Daivobet
- If you are allergic (hypersensitive) to calcipotriol, betamethasone or any of the other ingredients of Daivobet
- If you have problems with calcium levels in the body (ask your doctor)
- If you have certain types of psoriasis: these are erytrodermic, exfoliative and pustular (ask your doctor).

As Daivobet contains a strong steroid do NOT use on skin affected by
- infections caused by viruses (e.g. cold sores or chicken pox)
- infections caused by a fungus (e.g. athlete's foot or ringworm)
- infections caused by bacteria
- infections caused by parasites (e.g. scabies)
- tuberculosis (TB) or syphilis
- perioral dermatitis (red rash around the mouth)
- thin skin, easily damaged veins, stretch marks
- ichthyosis (dry skin with fish-like scales)
- acne (pimples)
- rosacea (severe flushing or redness of the skin on the face)
- ulcers or broken skin
- itching of the anus (back passage) or genitals (sex organs).

Take special care with Daivobet

Before using this medicine, tell your doctor/nurse/pharmacist if
- you are using other medicines that contain corticosteroids, as you may get side effects
- you have used this medicine for a long time and plan to stop (as there is a risk your psoriasis will get worse or 'flare up' when steroids are stopped suddenly)
- you have diabetes mellitus (diabetes), as your blood sugar/glucose level may be affected by the steroid
- your skin becomes infected, as you may need to stop your treatment
- you have a certain type of psoriasis called guttate psoriasis
- you have serious liver or kidney disease.

Special precautions
- Avoid use on more than 30 % of your body or using more than 15 grams per day
- Avoid using under bandages or dressings as it increases the absorption of the steroid
- Avoid use on large areas of damaged skin or skin folds (groin, armpits, under breasts) as it increases the absorption of the steroid
- Avoid use on the face or genitals (sex organs) as they are very sensitive to steroids
- Avoid excessive sunbathing, excessive use of solarium and other forms of light treatment.

Children
Daivobet is not recommended for the use in children below the age of 18 years.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Do not use Daivobet if you are pregnant (or might be pregnant) or if you are breast-feeding, unless you have agreed it with your doctor first. If your doctor has agreed that you can breast-feed, take care and do not apply Daivobet to the breast area.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine should not have any effect on your ability to drive or use machines.

3. HOW TO USE DAIVOBET

Always use Daivobet exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How to put on Daivobet: Cutaneous use.

Instruction for proper use
- Use only on your psoriasis and do not use on skin which does not have psoriasis
- Remove the cap and check that the seal in the tube is not broken before you first use the ointment
- To break the seal, use the point in the back of the cap
- Squeeze the ointment onto a clean finger
- Rub gently into your skin to cover the affected area of psoriasis until most of the ointment has disappeared into the skin
- Do not bandage, tightly cover or wrap the treated skin area
- Wash your hands well after using Daivobet (unless you are using the ointment to treat your hands). This will avoid accidentally spreading the ointment to other parts of your body (especially the face, scalp, mouth and eyes)
- Do not worry if some ointment accidentaly gets on normal skin near your psoriasis, but wipe it off if it spreads too far

- In order to achieve optimal effect, it is recommended not to take a shower or bath immediately after application of Daivobet ointment
- After applying the ointment avoid contact with textiles which are easily stained by grease (e.g. silk).

Duration of treatment
- Use the ointment once a day. It may be more convenient to use the ointment in the evening
- The normal initial treatment period is 4 weeks but your doctor may decide on a different treatment period
- Your doctor may decide on repeated treatment
- Do not use more than 15 grams in one day**.**

If you use other calcipotriol containing medicines, the total amount of calcipotriol medicines must not exceed 15 grams per day and the area treated should not exceed 30 % of the total body surface.

What should I expect when I use Daivobet?
Most patients see obvious results after 2 weeks, even if the psoriasis is not yet cleared at that point.

If you have used more Daivobet than you should
Contact your doctor if you have used more than 15 grams in one day.
Excessive prolonged use of Daivobet may cause a problem with calcium in your blood, which usually normalises when discontinuing treatment.
Your doctor may need to carry out blood tests to check that using too much ointment has not caused a problem with calcium in your blood.
Excessive prolonged use can also cause your adrenal glands to stop working properly (these are found near the kidneys and produce hormones).

If you forget to use Daivobet
Do not take a double dose to make up for forgotten individual doses.

If you stop using Daivobet
The use of Daivobet should be stopped as indicated by your doctor. It may be necessary for you to stop this medicine gradually, especially if you have used it for a long time.

If you have any further questions about the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Daivobet can cause side effects, although not everybody gets them.

Approximately 1 in 10 people may experience side effects but most of these are reactions at the site where the ointment has been applied and are usually mild and temporary.

Serious side effects
The following serious effects have been reported for Daivobet:
Uncommon (affects less than 1 in 100 people)
- Worsening of your psoriasis. If your psoriasis gets worse, tell your doctor as soon as possible.

Rare (affects less than 1 in 1,000 people)
- Pustular psoriasis may occur (a red area with yellowish pustules usually on the hands or feet). If you notice this, stop taking Daivobet and tell your doctor as soon as possible.

Some serious side effects are known to be caused by betamethason**e** (a strong steroid), one of the ingredients in Daivobet. You should tell your doctor as soon as possible if any of the serious side effects occur:
- Your adrenal glands may stop working properly. Signs are tiredness, depression and anxiety.

- Cataracts (signs are cloudy and foggy vision, difficulty seeing at night and sensitivity to light) or an increase in pressure inside the eye (signs are eye pain, red eye, decreased or cloudy vision)
- Infections (because your immune system which fights infections may be suppressed or weakened)
- Impact on the metabolic control of diabetes mellitus (if you have diabetes you may experience fluctuations in the blood glucose levels).

These side effects are more likely to happen after long-term use, use in skin folds (e.g. groin, armpits or under breasts), use under bandages or dressings or use on large areas of skin.

Serious side effects known to be caused by calcipotriol
- Allergic reactions with deep swelling of the face or other parts of the body such as the hands or feet. Swelling of the mouth/throat and trouble breathing may occur. If you have an allergic reaction, stop taking Daivobet, tell your doctor immediately or go to the casualty department at your nearest hospital
- Treatment with this ointment may cause the level of calcium in your blood or urine to increase (usually when too much ointment has been used). Signs of increased calcium in blood is bone pain, constipation, poor appetite, nausea and vomiting. This can be serious and you should contact your doctor as soon as possible. However, when the treatment is stopped, the levels return to normal.

<u>Less serious side effects</u>
The following less serious side effects have been reported for Daivobet. If any of them last a long time or cause you problems, you should tell your doctor or nurse.
Common side effects (affect less than 1 in 10 people)
- Itching
- Rash
- Burning sensation.

Uncommon (affect less than 1 in 100 people)
- Skin pain or irritation
- Rash with inflammation of the skin (dermatitis)
- Redness of the skin due to widening of the small blood vessels (erythema)
- Inflammation or swelling of the hair root (folliculitis)
- Changes in skin colour in the area you have used the ointment.

Not known frequency
- Rebound effect: A worsening of symptoms/psoriasis after ended treatment.

Less serious side effects caused by using betamethasone, include the following. You should tell your doctor as soon as possible if you notice them.
- Thinning of the skin
- Appearance of surface blood vessels or stretch marks
- Changes in hair growth
- Red rash around the mouth (perioral dermatitis)
- Skin rash with inflammation or swelling (allergic contact dermatitis)
- Shiny brown gel-filled bumps (colloid milia)
- Lightening of skin colour (depigmentation).

Less serious side effects known to be caused by calcipotriol include the following
- Dry skin
- Sensitivity of the skin to light resulting in a rash has also been reported
- Eczema.

If you notice the above or any other changes in your health while taking this medicine, tell your doctor.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DAIVOBET

- Keep out of the reach and sight of children
- Do not use Daivobet after the expiry date, which is stated on the label after EXP. The expiry date refers to the last day of that month
- Do not store the medicine above 25 °C
- The tube should be discarded 1 year after first opening. Write the date you first opened the tube in the space provided on the carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Daivobet contains
The active substances are:
Calcipotriol and betamethasone.
One gram of ointment contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

The other ingredients are:
- liquid paraffin
- all-rac-α-tocopherol
- polyoxypropylene-15-stearyl ether
- white soft paraffin.

What Daivobet looks like and contents of the pack
Daivobet ointment is an off-white to yellow coloured ointment filled in aluminium/epoxyphenol tubes with polyethylene screw cap.
Pack sizes: 15, 30, 60, 100 and 120 g.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation holder is:
[See Annex I - To be completed nationally]

The manufacturer is:
LEO Laboratories Ltd.
Cashel Road, Dublin 12, Ireland.

For further information about this medicine, contact the local representative of the Marketing Authorisation Holder
[To be completed nationally]

This medicine is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

Detailed information on this medicine is available on the web site of {name of MS/Agency}

PACKAGE LEAFLET: INFORMATION FOR THE USER

Daivobet and associated names (see Annex I) **50 micrograms/0.5 mg/g gel**
[See Annex I - To be completed nationally]
calcipotriol/betamethasone

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT DAIVOBET IS AND WHAT IT IS USED FOR

Daivobet is used as topical treatment of scalp psoriasis in adults and on the skin of other body areas to treat mild to moderate plaque psoriasis (psoriasis vulgaris) in adults**.** Psoriasis is caused by your skin cells being produced too quickly. This causes redness, scaling and thickness of your skin.

Daivobet contains calcipotriol and betamethasone. Calcipotriol helps to bring the rate of skin cell growth back to normal and betamethasone acts to reduce inflammation.

2. BEFORE YOU USE DAIVOBET

Do not use Daivobet
- If you are allergic (hypersensitive) to calcipotriol, betamethasone or any of the other ingredients of Daivobet
- If you have problems with calcium levels in your body (ask your doctor)
- If you have certain types of psoriasis: these are erythrodermic, exfoliative and pustular (ask your doctor).

As Daivobet contains a strong steroid do NOT use it on skin affected by
- infections caused by viruses (e.g. cold sores or chicken pox)
- infections caused by a fungus (e.g. athlete's foot or ringworm)
- infections caused by bacteria
- infections caused by parasites (e.g. scabies)
- tuberculosis (TB) or syphilis
- perioral dermatitis (red rash around the mouth)
- thin skin, easily damaged veins, stretch marks
- ichthyosis (dry skin with fish-like scales)
- acne (pimples)
- rosacea (severe flushing or redness of the skin on the face)
- ulcers or broken skin
- itching of the anus (back passage) or genitals (sex organs).

Take special care with Daivobet

Before using this medicine, tell your doctor/nurse/ pharmacist if
- you are using other medicines that contain corticosteroids as you may get side-effects
- you have used this medicine for a long time and plan to stop (as there is a risk your psoriasis will get worse or 'flare up' when steroids are stopped suddenly)
- you have diabetes mellitus (diabetes) as your blood sugar/glucose level may be affected by the steroid
- your skin becomes infected as you may need to stop your treatment
- you have a certain type of psoriasis called guttate psoriasis
- you have serious liver or kidney disease.

Special precautions
- Avoid use on more than 30 % of your body or using more than 15 grams per day
- Avoid using under a batching cap, bandages or dressings as it increases the absorption of the steroid
- Avoid use on large areas of damaged skin or skin folds (groin, armpits, under breasts) as it increases the absorption of the steroid
- Avoid use on your face or genitals (sex organs) as they are very sensitive to steroids
- Avoid excessive sunbathing, excessive use of solarium and other forms of light treatment.

Children
Daivobet is not recommended for the use in children below the age of 18 years.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Do not use Daivobet if you are pregnant (or might be pregnant) or if you are breast-feeding, unless you have agreed it with your doctor first. If your doctor has agreed that you can breast-feed, take care and do not apply Daivobet to the breast area.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine should not have any effect on your ability to drive or use machines.

Important information about some of the ingredients of Daivobet
Daivobet contains butylated hydroxytoluene (E321), which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

3. HOW TO USE DAIVOBET

Always use Daivobet exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How to put on Daivobet: Cutaneous use.

Instructions for proper use
- Use only on your psoriasis and do not use on skin which does not have psoriasis
- Shake the bottle before use and remove the cap
- Squeeze the gel onto a clean finger or directly onto the area affected by psoriasis.
- Apply Daivobet to the affected area with your fingertips, and rub it in gently until the area affected by psoriasis is covered by a thin layer of gel.
- Do not bandage, tightly cover or wrap the treated skin area
- Wash your hands well after using Daivobet. This will avoid accidentally spreading the gel to other parts of your body (especially the face, mouth and eyes)

- Do not worry if some gel accidentally gets on normal skin near your psoriasis, but wipe it off if it spreads too far
- In order to achieve optimal effect, it is recommended not to take a shower or bath immediately after application of Daivobet gel
- After applying the gel, avoid contact with textiles which are easily stained by grease (e.g. silk).

If you have scalp psoriasis
- Before applying Daivobet to the scalp, comb the hair to remove any loose scales. Tilt your head to make sure Daivobet does not run onto your face. It may help to part your hair before you use Daivobet. Apply Daivobet to the affected area with your fingertips, and rub it in gently
- For treatment of the scalp usually an amount between 1 g and 4 g per day is sufficient (4 g corresponds to one teaspoon)
- Washing your hair before application of Daivobet is not necessary
- In order to achieve optimal effect, it is recommended that the hair is not washed immediately after application of Daivobet. Let Daivobet remain on the scalp during the night or during the day.

Duration of treatment
- Use the gel once a day. It may be more convenient to use the gel in the evening
- The normal initial treatment period is 4 weeks for scalp areas and 8 weeks for non-scalp areas
- Your doctor may decide on a different treatment period
- Your doctor may decide on repeated treatment
- Do not use more than 15 grams in one day.

If you use other calcipotriol containing medicines, the total amount of calcipotriol medicines must not exceed 15 grams per day and the area treated should not exceed 30 % of the total body surface.

What should I expect when I use Daivobet?
Most patients see obvious results after 2 weeks, even if the psoriasis is not yet cleared at that point.

If you have used more Daivobet than you should
Contact your doctor if you have used more than 15 grams in one day.
Excessive prolonged use of Daivobet may also cause a problem with calcium in your blood, which usually normalises when discontinuing treatment.
Your doctor may need to carry out blood tests to check that using too much gel has not caused a problem with calcium in your blood.
Excessive prolonged use can also cause your adrenal glands to stop working properly (the adrenal glands are found near the kidneys and produce hormones).

If you forget to use Daivobet
Do not take a double dose to make up for forgotten individual doses.

If you stop using Daivobet
The use of Daivobet should be stopped as indicated by your doctor. It may be necessary for you to stop this medicine gradually, especially if you have used it for a long time.

If you have any further questions about the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Daivobet can cause side effects, although not everybody gets them.

Approximately 1 in 12 people may experience side effects, but most of these are reactions at the site where the gel has been applied.

Serious side effects

Tell your doctor/nurse immediately or as soon as possible if any of the following happens. You may have to stop your treatment.
The following serious side effects have been reported for Daivobet
Uncommon (affect less than 1 in 100 people)
- Worsening of your psoriasis. If your psoriasis gets worse, tell your doctor as soon as possible.

Some serious side effects are known to be caused by betamethasone (a strong steroid), one of the ingredients in Daivobet. You should tell your doctor as soon as possible if any of the serious side effects occur. These side effects are more likely to happen after long-term use, or use under occlusion. The side effects include the following:
- Your adrenal glands may stop working properly. Signs are tiredness, depression and anxiety.
- Cataracts (signs are cloudy and foggy vision, difficulty seeing at night and sensitivity to light) or an increase in pressure inside your eye (signs are eye pain, red eye, decreased or cloudy vision)
- Infections (because your immune system, which fights infections, may be suppressed or weakened)
- Pustular psoriasis (a red area with yellowish pustules usually on the hands or feet). If you notice this, stop taking Daivobet and tell your doctor as soon as possible
- Impact on the metabolic control of diabetes mellitus (if you have diabetes you may experience fluctuations in the blood gluclose levels).

Serious side effects known to be caused by calcipotriol
- Allergic reactions with deep swelling of the face or other parts of the body such as the hands or feet. Swelling of the mouth/throat and trouble breathing may occur. If you have an allergic reaction, stop taking Daivobet, tell your doctor immediately or go to the casualty department at your nearest hospital
- Treatment with this gel may cause the level of calcium in your blood or urine to increase (usually when too much gel has been used). Signs of increased calcium in blood is bone pain, constipation, poor appetite, nausea and vomiting. This can be serious, and you should contact your doctor immediately. However, when the treatment is stopped, the levels return to normal.

<u>Less serious side effects</u>
The following less serious side effects have been reported for Daivobet
Common side effects (affect less than 1 in 10 people)
- Itching.

Uncommon (affect less than 1 in 100 people)
- Eye irritation
- Burning sensation of the skin
- Skin pain or irritation
- Inflammation or swelling of the hair root (folliculitis)
- Rash with inflammation of the skin (dermatitis)
- Redness of the skin due to widening of the small blood vessels (erythema)
- Acne (pimples)
- Dry skin
- Rash
- Pustular rash.

Less serious side effects caused by using betamethasone for a long time, include the following, and you should tell your doctor or nurse as soon as possible if you notice any of them
- Thinning of the skin
- Appearance of surface veins or stretch marks
- Changes in hair growth
- Red rash around the mouth (perioral dermatitis)
- Skin rash with inflammation or swelling (allergic contact dermatitis)
- Small white spots (colloid milia)
- Depigmentation (lightening of skin colour).

Less serious side effects known to be caused by calcipotriol include the following
- Sensitivity of the skin to light resulting in a rash
- Eczema.

If you notice the above or any other changes in your health while taking this medicine, tell your doctor.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DAIVOBET

- Keep out of the reach and sight of children
- Do not use Daivobet after the expiry date, which is stated on the bottle after EXP. The expiry date refers to the last day of that month
- Do not refrigerate. Keep the bottle in the outer carton in order to protect from light
- Discard the bottle with any remaining gel 3 months after first opening.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Daivobet contains
The active substances are:
Calcipotriol and betamethasone.
One gram of gel contains 50 micrograms of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate).

The other ingredients are:
- paraffin, liquid
- polyoxypropylene-15 stearyl ether
- castor oil, hydrogenated
- butylhydroxytoluene (E321)
- all-rac-α-tocopherol.

What Daivobet looks like and the contents of the pack
Daivobet is an almost clear, colourless to slightly off-white gel filled in high-density polyethylene bottles with low-density polyethylene nozzle and a high-density polyethylene screw cap.
The bottles are placed in cartons.
Pack sizes: 15, 30, 60 and 2 x 60 g.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation holder is:
[See Annex I - To be completed nationally]

The manufacturer is:
LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S)
Industriparken 55
DK-2750 Ballerup
Denmark

For further information about this medicine, contact the local representative of the Marketing Authorisation Holder
[To be completed nationally]

This medicine is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

Detailed information on this medicine is available on the web site of {name of MS/Agency}