Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dovobet 50 micrograms/0.5mg/g ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ointment.

Product imported from the UK:
Off-white to yellow ointment.

Product imported from Italy:
Off-white to yellow ointment.

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
Dovobet ointment should be applied to the affected area once daily. The recommended treatment period is 4 weeks. There is experience with repeated courses of Dovobet 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 Dovobet ointment in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

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

Method of administration
Dovobet 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 Dovobet ointment.

4.3 Contraindications

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

Dovobet ointment is contraindicated in erythrodermic, exfoliative and pustular psoriasis.
Due to the content of calcipotriol Dovobet ointment is contra-indicated in patients with known disorders of calcium metabolism.
Due to the content of corticosteroid Dovobet 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
Dovobet 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 Dovobet gel (scalp application) and high doses of Dovobet 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 Dovobet ointment in guttate psoriasis.

Concurrent treatment and UV exposure
There is no experience for the use of this medicinal product on the scalp. Dovobet ointment for body psoriasis lesions has been used in combination with Dovobet gel for scalp psoriasis lesions, but there is no experience of combination of

Dovobet with other topical anti-psoriatic products at the same
treatment area, other anti-psoriatic medicinal products administered systemically or with phototherapy.
During Dovobet 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 Dovobet 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, Dovobet ointment should only be used when the potential benefit justifies the potential risk.

Breast-feeding
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 Dovobet ointment to women who breast-feed. The patient should be instructed not to use Dovobet 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

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

4.8 Undesirable effects

The trial programme for Dovobet 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 Dovobet 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 Dovobet 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 Dovobet ointment used once daily as required, either alone or alternating with Dovonex, for up to 52 weeks, compared with Dovonex used alone for 48 weeks after an initial course of Dovobet ointment. Adverse drug reactions were reported by 21.7 % of the patients in the Dovobet ointment group, 29.6 % in the Dovobet ointment/Dovonex alternating group and 37.9 % in the Dovonex group. The adverse drug reactions that were reported by more than 2 % of the patients in the Dovobet 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 Dovobet ointment group, 2.8 % in the Dovobet ointment/Dovonex alternating group and 2.9 % in the Dovonex 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 Dovobet gel and Dovobet 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 Dovobet 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 Dovobet ointment 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. 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 Dovobet gel and Dovobet 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

Unopened container: The shelf life expiry date of this product is the date shown on the tube and outer carton of the product as marketed in the country of origin.

After first opening of container: 12 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Product imported from the UK:
Over-labelled carton containing an Aluminium/epoxyphenol tube with polyethylene screw cap.
Tube size: 60g.

Product imported from Italy:
Carton containing two Aluminium/epoxyphenol tube with polyethylene screw cap.
Tube sizes: 2 x 30g.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/62/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th June 2010

10 DATE OF REVISION OF THE TEXT

February 2012