Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dovobet 50 microgram/g + 0.5 mg/g ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of Dovobet contains 50microgram calcipotriol (as hydrate) and 0.5mg betamethasone (as dipropionate).

Excipient with known effects:
Butylhydroxytoluene (E321) 50 micrograms/g ointment
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ointment
Product imported from the United Kingdom:
Off-white to yellow ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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.
Currently available data in children aged 12 to 17 years are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

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, when 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 light. 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
Dovobet ointment contains butylhydroxytoluene (E321). This 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 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 and <1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Skin and subcutaneous tissue disorders
Common: Pruritus

Common: Rash
Common: Burning sensation of skin
Uncommon: Exacerbation of psoriasis
Uncommon: Skin pain or irritation
Uncommon: Dermatitis
Uncommon: Erythema
Uncommon: Folliculitis
Uncommon: 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).

Paediatric population

In an uncontrolled open study, 33 adolescents aged 12-17 years with psoriasis vulgaris were treated with Dovobet ointment for 4 weeks to a maximum of 56 g per week. No new adverse events were observed and no concerns regarding the systemic corticosteroid effect were identified. The size of the study does not however allow firm conclusions regarding the safety profile of Dovobet ointment in children and adolescents.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via ‘freepost’, in addition to the traditional post-paid ‘yellow card’ option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O’Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

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 (maximum dose 100 g weekly, cf. section 4.2 and 4.4) for 5 months 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 immunosuppressive 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.

Paediatric population
The adrenal response to ACTH challenge was measured in an uncontrolled 4-week study in 33 adolescents aged 12-17 years with body psoriasis who used up to 56 g per week of Dovobet ointment. No cases of HPA axis suppression were reported. No hypercalcaemia was reported but one patient had a possible treatment related increase in urinary calcium.

5.2 Pharmacokinetic properties

Clinical studies with radiolabelled ointment indicate that the systemic absorption of calcipotriol and betamethasone from Dovobet 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 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 tumors.
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
Butylhydroxytoluene (E321)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.
This product should be discarded 12 months after first opening.

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 in a cardboard outer. Tube size 120g.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
Unit L2
North Ring Business Park
Santry
Dublin 9

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/053/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 18th January 2008

10 DATE OF REVISION OF THE TEXT

February 2014