Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dovobet 50 microgram/g + 0.5 mg/g Ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Calcipotriol 50 microgram/g (as hydrate), betamethasone 0.5 mg/g (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.

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 should be applied to the affected area once daily. The recommended treatment period is 4 weeks. After this period repeated treatment with Daivobet® can be initiated under medical supervision.

The maximum daily dose should not exceed 15 g, the maximum weekly dose should not exceed 100 g, and the treated area should not be more than 30% of the body surface.

Dovobet is not recommended for the use in children and adolescents below the age of 18 years.

4.3 Contraindications

Known hypersensitivity to the active substances or to any of the excipients.

Due to the content of calcipotriol Dovobet is contra-indicated in patients with known disorders of calcium metabolism.

Due to the content of corticosteroid Dovobet 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, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers, wounds, perianal and genital pruritus.

Dovobet is contraindicated in guttate, erythrodermic, exfoliative and pustular psoriasis.

Dovobet is contraindicated in patients with severe renal insufficiency or severe hepatic disorders.

4.4 Special warnings and precautions for use

The patient must be instructed in correct use of the product to avoid application and accidental transfer to the scalp, face, mouth and eyes. Hands must be washed after each application.

Treatment of more than 30% of the body surface should be avoided.

The risk of hypercalcaemia is minimal when the recommendations relevant to calcipotriol are fulfilled. Due to the content of calcipotriol hypercalcaemia may occur if the maximum weekly dose (100g) is exceeded. Serum calcium is quickly normalised, however, when treatment is discontinued.

Dovobet contains a strong potent group III-steroid and concurrent treatment with other steroids must be avoided. Adverse effects 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 on large areas of damaged skin and under occlusive dressings or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of corticosteroids. Skin of the face and genitals are very sensitive to corticosteroids. Long-term treatment of these parts of the body should be avoided. These areas should only be treated with the weaker corticosteroids.
When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, when infection worsens, treatment with corticosteroids should be stopped.

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.

With long-term use there is an increased risk of local and systemic corticosteroid undesirable effects. The treatment should be discontinued in case of undesirable effects related to long-term use of corticosteroid, see section 4.8, Undesirable effects.

There may be a risk of rebound when discontinuing a long-term treatment with corticosteroids.

There is no experience for the use of this product on the scalp. There is no experience with concurrent use of other anti-psoriatic products administered locally or systemically or phototherapy.

During Dovobet 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 UV radiation only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3, preclinical safety data).

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Dovobet in pregnant women. Studies in animals with glucocorticoids have shown reproductive toxicity (see section 5.3, preclinical safety data), 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 should only be used when the potential benefit justifies the potential risk.

Lactation
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 to women who breast feed. The patient should be instructed not to use Dovobet on the breast when breast feeding.

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

Very common	>1/10
Common	>1/100 and <1/10
Uncommon	>1/1,000 and <1/100
Rare	>1/10,000 and <1/1000
Very rare	<1/10,000

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.

Based on data from clinical trials and postmarket 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 undesirable effects are listed by MedDRA SOC and the individual undesirable effects are listed starting with the most frequently reported.

- Skin and subcutaneous tissue disorders

Common:	Pruritus
Common:	Rash
Common:	Burning sensation of skin
Uncommon:	Skin pain or irritation
Uncommon:	Dermatitis
Uncommon:	Erythema
Uncommon:	Exacerbation of psoriasis
Uncommon:	Folliculitis
Uncommon:	Application site pigmentation changes
Rare:	Pustular psoriasis

Undesirable effects observed for calcipotriol and betamethasone, respectively:

Calcipotriol
Undesirable effects 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, cf. section 4.4, Special warnings and precautions for use.

Betamethasone (as dipropionate)

This product contains a potent corticosteroid.
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 effects due to topical use of corticosteroids are rare in adults, however they can be severe. Adrenocortical suppression, cataract, infections and increase of intra-ocular pressure can occur, especially after long term treatment. Systemic effects occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long term treatment, cf. section 4.4, Special warnings and precautions for use.

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, Posology and method of administration and section 4.4, Special warnings and precautions for use) for 5 months developed Cushing's syndrome and pustular psoriasis after abruptly stopping treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DO5AX52 Calcipotriol, combinations.

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 (approximately by a factor of 10). 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 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. Adverse drug reactions were reported by 21.7% of the patients in the Dovobet group, 29.6% in the Dovobet/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 group were pruritus (5.8%) and psoriasis (5.3%).

Adverse events of concern possibly related to long-term corticosteroid use were reported by 4.8% of the patients in the Dovobet group, 2.8% in the Dovobet/Dovonex alternating group and 2.9% in the Dovonex group.

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%. 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. Excretion takes place by urine and faeces.

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 was detected. Moreover reduction in offspring survival, in body weight and body weight gain was observed. There was no impairment of fertility. The relevance for humans is unknown.

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

In a study where albino hairless mice were repeatedly exposed to both ultraviolet (UV) radiation and dermally administered calcipotriol for 40 weeks at dose levels corresponding to 9, 30 and 90 µg/m^2/day (equivalent to 0.25, 0.84, 2.5 times the maximum recommended daily dose for a 60 kg adult, respectively), a reduction in the time required for UV radiation to induce the formation of skin tumours was observed (statistically significant in males only), suggesting that calcipotriol may enhance the effect of UV radiation to induce skin tumours. The clinical relevance of this finding is unknown.
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
Alpha-tocopherol
White soft paraffin

6.2 Incompatibilities

Not to be mixed with other medicinal products.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the over labelled tube and outer carton of the product on the market in the country of origin, after EXP.

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

Aluminium/epoxyphenol over labelled tubes with polyethylene screw cap.

Tube sizes: 60 and 120 g.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

McDowell Pharmaceuticals
4 Altona Road
Lisburn, BT27 5QB
N. Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1473/47/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th November 2010

10 DATE OF REVISION OF THE TEXT