Attachment 1: Product information for AusPAR Daivobet 50/500; calcipotriol 50 µg/g and betamethasone (as dipropionate) 500 µg/g gel; Leo Pharma Pty Ltd; PM-2011-04144-3-5; Date of Finalisation 9 August 2013. This Product Information was approved at the time this AusPAR was published.

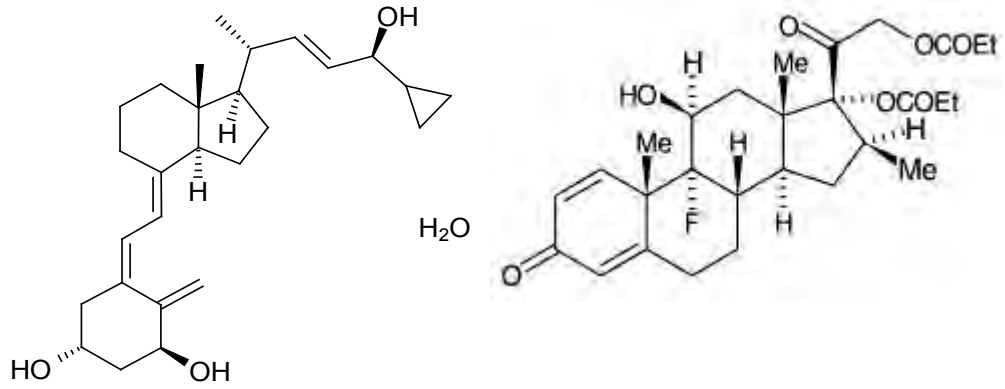
PRODUCT INFORMATION

Daivobet® 50/500 gel

Calcipotriol 50 microgram/g
Betamethasone 500 microgram/g present as dipropionate AUST R 161936

NAME OF THE MEDICINE:

Daivobet® 50/500 gel



Calcipotriol Betamethasone dipropionate

Calcipotriol is (1S, 3R, 5Z, 7E, 22E, 24S) -24-Cyclopropyl-9, 10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol (CAS no.: 112828-00-9). The molecular weight of calcipotriol hydrate is 430.6.

Betamethasone dipropionate is 9-fluoro-11b, 17, 21-trihydroxy-16b-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate (CAS no.: 5593-20-4). The empirical formula is $C_{28}H_{37}FO_7$. The molecular weight of betamethasone dipropionate is 504.6.

DESCRIPTION

Daivobet® gel is an almost clear, colourless to slightly off-white gel and contains 50 microgram/g calcipotriol and 500 microgram/g betamethasone (as dipropionate).

Calcipotriol is a white or almost white crystalline substance. It is freely soluble in ethanol, soluble in chloroform and propylene glycol, particularly insoluble in liquid paraffin. Solubility in water is 0.6 mg/mL and the melting point is 166 to 168ºC. Calcipotriol is a vitamin D derivative and behaves in a similar manner to vitamin D, forming a reversible temperature-dependent equilibrium between calcipotriol and pre-calcipotriol.

Betamethasone dipropionate is a white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone and in methylene chloride, sparingly soluble in alcohol.

Daivobet® gel also contains paraffin-liquid, PPG-15 stearyl ether, hydrogenated castor oil,

butylated hydroxyl toluene (E321) and alpha tocopherol.

PHARMACOLOGY

Pharmacodynamics

Calcipotriol is a non-steroidal antipsoriatic agent, derived from vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the 1, $25(OH)_2D_3$ receptor. Calcipotriol is as potent as $1,25(OH)_2D_3$, the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than $1,25(OH)_2D_3$ in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation (without any evidence of a cytotoxic effect) of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalisation of epidermal growth.

Betamethasone dipropionate is a potent topically-active corticosteroid producing prompt, marked and prolonged anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties, without curing the underlying condition. These effects can be enhanced under occlusive conditions due to increased penetration of stratum corneum (by approximately a factor of 10). The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.

Pharmacokinetics

The systemic exposure to calcipotriol and betamethasone dipropionate from topically applied Daivobet® gel is 13 – 45% less than 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.

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised. The main route of excretion of calcipotriol and betamethasone dipropionate is via faeces (rats, mice and minipigs).

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.

CLINICAL TRIALS

Efficacy

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.

Table 1: Efficacy of once daily use of Daivobet® gel in adults compared to the individual active components in the same gel formulation

% 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)

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 (clear or minimal disease according to the IGA at week 8) showed that Daivobet® gel was statistically significantly more effective than Daivonex® Scalp Solution.

Table 2: Efficacy of Daivobet® gel in adults compared to Daivonex® Scalp Solution

% of patients with clear or minimal 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)

One multicenter, randomised, double-blind study was conducted in subjects with psoriasis vulgaris on body areas. In this study, 1152 subjects were randomised to one of four treatment groups: Daivobet® gel, betamethasone dipropionate in the same optimised vehicle, calcipotriol in the same optimised vehicle, or the optimised vehicle alone. The study enrolled subjects with mild to moderate psoriasis vulgaris on the body. The majority of subjects had disease of moderate severity at baseline. Subjects were treated once daily for 8 weeks.

Efficacy was assessed as the proportion of subjects at week 4 and week 8 who were "clear" or "almost clear" and improved at least two steps according to an Investigator's Global Assessment of Diseases Severity. Table 3 contains the response rates in this trial.

Table 3: Percentage of Patients with Clear or Almost Clear Disease and at least Two Steps Improvement According to the Investigator's Global Assessment of Disease Severity

	Daivobet® gel (n=482)	Betamethasone Dipropionate in vehicle (n=479)	Calcipotriol in vehicle (n=96)	Vehicle (n=95)
Week 4	13.3%	12.5%[1]	5.2%[2]	2.1%[2]
Week 8	29.0%	21.5%[2]	14.6%[2]	6.3%[2]

[1] No statistically significant difference to Daivobet® gel (P=0.82)
[2] Statistically significantly less effective than Daivobet® gel (P≤0.019)

Safety

A randomised, double-blind long-term clinical study including 869 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.

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.

In another study, 43 subjects were treated with Daivobet® gel on body areas and any affected areas on the scalp. Adrenal suppression was identified in 3 of 43 subjects (7%) after 4 weeks of treatment and in 0 of 36 subjects who provided data after 8 weeks treatment. The results from this limited number of subjects demonstrated that Daivobet® gel may have effects on the HPA axis but the incidence was low and did not increase over time even in a maximum use setting. See Overdosage section for additional information.

The effects on calcium metabolism were also studied in these patients. The results demonstrated that there were no changes of clinical concern regarding the effect on calcium metabolism.

INDICATIONS

Topical treatment of scalp psoriasis.

Topical treatment of mild to moderate plaque psoriasis on the body in adults.

CONTRAINDICATIONS

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

ii Patients with known disorders of calcium metabolism.

iii Due to the corticosteroid content: viral lesions of the skin (eg herpes or varicella), fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis or syphilis, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, rosacea, ulceration and wounds, perianal and genital pruritus.

iv Guttate, erythrodermic, exfoliative and pustular psoriasis

v Patients with severe renal insufficiency or severe hepatic disorders.

PRECAUTIONS

Treatment of more than 30% of the body surface should be avoided. Repeated treatment of large body surface areas may result in adverse effects.

Uncommon local adverse reactions (such as eye irritation or irritation of facial skin) were observed, when the drug was accidentally administered in the area of face, or accidentally to the eyes or conjunctives (see Adverse Effects section). The patient must be instructed in correct use of the 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 unless affected skin on the hands is being treated.

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.

Daivobet® gel contains a potent WHO group III steroid and concurrent treatment with other steroids on the scalp 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 under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids.

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.

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. Skin of the face and genitals are very sensitive to corticosteroids. These areas should only be treated with weaker corticosteroids.

The gel should be applied to the affected areas of the scalp once daily for up to 4 weeks

and affected areas of the body once daily for up to 8 weeks. If no response is observed after 4 weeks then treatment of the body psoriasis should be ceased. Treatment of body psoriasis should be ceased after 8 weeks, as there are no long-term efficacy data available beyond 8 weeks in patients treated with Daivobet® gel on the body. However, there are safety data on intermittent courses of Daivobet® gel used for up to 52 weeks for scalp psoriasis. With long-term use there is an increased risk of local and systemic corticosteroid undesirable effects, including hypothalamic pituitary adrenal (HPA) axis suppression. The treatment should be discontinued in case of undesirable effects related to long-term use of corticosteroid (see Adverse Effects section). There may be a risk of rebound when discontinuing long-term treatment with corticosteroids. Medical supervision should therefore continue in the post-treatment period.

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

Due to the content of calcipotriol, hypercalcaemia may occur if the maximum weekly dose (100 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.

The stability of calcipotriol in sunlight and UV light has not been demonstrated. No clinical trials have been conducted with calcipotriol-containing products in Australia, where there is a particularly high potential to be exposed to high levels of UV radiation. In addition, the phototoxic effects of Daivobet® gel have not been studied in psoriasis patients. Therefore, treated skin areas should be protected from sunlight and UV light (using physical covering and/or sunscreens), particularly where exposure may be considerable for reasons such as occupation.

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

Carcinogenicity

A dermal carcinogenicity study with calcipotriol in mice showed no indications of increased carcinogenic risks. Calcipotriol solution was applied topically for up to 24 months at doses of 3, 10 and 30 µg/kg/day (corresponding to 9, 30 and 90 µg/m^2/day). The high-dose was considered to be the Maximum Tolerated Dose for dermal treatment of mice with calcipotriol. Survival was decreased at 10 and 30 µg/kg/day, particularly in the males. The reduced survival was associated with an increased incidence of renal lesions. This is an expected effect of treatment with high doses of calcipotriol or other vitamin D analogues. There were no dermal effects and no dermal or systemic carcinogenicity.

In a study where albino hairless mice were repeatedly exposed to both ultraviolet (UV) radiation and topically applied calcipotriol for 40 weeks at the same dose levels as in the dermal calcipotriol carcinogenicity study, 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. In a supplementary study, mice of the same strain were treated repeatedly with either calcipotriol solution or calcipotriol/betamethasone gel, followed by irradiation with UVR and measurement of recognised cellular indicators of skin photocarcinogenicity. This study showed a similar enhancing effect of calcipotriol alone on the photobiological

response of the skin calcipotriol/betamethasone gel increased cellular proliferation but did not increase other markers indicative of enhancement of photocarcinogenesis. The clinical relevance of these findings is unknown.

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

Genotoxicity

Calcipotriol was not genotoxic in assays for gene mutations (Ames test and mouse lymphoma TK locus assay) or chromosomal damage (human lymphocyte chromosomal aberration or mouse micronucleus test). Betamethasone dipropionate was not genotoxic in the Ames mutagenicity assay, the mouse lymphoma TK locus assay or in the rat micronucleus test.

Use in Pregnancy (Category B1)

There are no adequate data from the use of Daivobet® gel in pregnant women. Daivobet® gel should only be used during pregnancy when the potential benefit clearly outweighs the potential risk.

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. Studies of calcipotriol in animals have shown an increase in the incidence of skeletal variations in rats (wavy ribs, extra ribs, incomplete development of skull bones) at oral doses of 18 mg/kg day and in rabbits (reduced skeletal ossification) at oral doses of 36 mg/kg day. The relevance of these findings for humans is unknown.

Effects on Fertility

Possible effects of betamethasone in combination with calcipotriol on fertility have not been investigated in animals. Studies of the oral administration of calcipotriol in rats have shown no impairment of fertility.

Use in Lactation

Betamethasone is excreted into breast milk. It is unknown if topical application of Daivobet® gel could result in sufficient systemic absorption to produce significant quantities of this corticosteroid in human breast milk. There are no data on the excretion of calcipotriol in breast milk.

Caution should be exercised when prescribing Daivobet® gel to breast-feeding women. Application of Daivobet® gel to the breast area should be avoided. Daivobet® gel should only be used during lactation if the potential benefits clearly outweigh the potential risks.

NOTE: After applying Daivobet® gel, mothers should wash their hands thoroughly prior to handling their child.

Use in Children

Daivobet® gel is not recommended for use in children and adolescents below 18 years of

age as the safety and effectiveness of Daivobet® gel in this population has not been established.

Because of a higher ratio of skin surface area to body mass, children under the age of 12 years may be at particular risk of systemic adverse effects when they are treated with topical corticosteroids.

Renal Impairment

Safety has not been established in patients with renal impairment. Daivobet® is contraindicated in patients with severe renal impairment.

Hepatic Impairment

Safety has not been established in patients with hepatic impairment. Daivobet® is contraindicated in patients with severe hepatic impairment.

Interactions with other drugs

No interaction studies have been performed.

There is no experience with concurrent use of other anti-psoriatic products administered systemically or with phototherapy.

Effects on Laboratory Tests

There are no data available on the effects of Daivobet® gel on laboratory tests.

ADVERSE EFFECTS

Clinical Trials

Definition of frequency of adverse events:

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

The clinical trial programme for Daivobet® gel has so far included more than 6, 000 patients of whom more than 3,000 were treated with Daivobet® gel.

Scalp Psoriasis

Approximately 8% of patients treated with Daivobet® gel on the scalp experienced a non-serious adverse drug reaction (possibly related to study medication).

Based on the above frequency definition, data from clinical trials show that the only

common adverse drug reaction is pruritus. The uncommon adverse events are burning sensation of the skin, skin pain or irritation, folliculitis, dermatitis, erythema, acne, dry skin, exacerbation of psoriasis, rash, pustular rash and eye irritation. These adverse events were all non-serious local reactions.

Body Psoriasis

Adverse drug reactions that occurred in more than 1% of patients treated with Daivobet® gel on the body areas are listed in Table 4.

Table 4: Adverse drug reactions occurring in >1% of subjects in the Daivobet® gel group of controlled studies in body psoriasis: safety analysis set

Preferred term	Daivobet® gel (N=824) n (%)	Betamethasone gel (N=562) n (%)	Calcipotriol gel (N=175) n (%)	Gel vehicle (N=226) n (%)
Pruritus	12 (1.5)	2 (0.4)	5 (2.9)	15 (6.6)

In a randomised, multicentre, active and vehicle controlled study where 482 patients applied Daivobet® gel to affected body areas for 8 weeks, no statistically significant differences in incidence of adverse drug reactions between the Daivobet® gel and vehicle were recorded.

There are inadequate data on relapse and rebound with Daivobet® gel. Adverse events observed for calcipotriol and betamethasone are provided below.

Calcipotriol

Potential adverse events include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, aggravation of psoriasis, transient photosensitivity, transient changes in skin pigmentation and allergic and hypersensitivity reactions including very rare cases of angioedema and facial oedema. After topical use, systemic effects, causing hypercalcaemia or hypercalciuria may appear very rarely.

Betamethasone

This product contains a potent corticosteroid.

Local reactions can occur after topical corticosteroid use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia. When used for the treatment of psoriasis, there may be the risk of generalised pustular psoriasis. There may be a risk of rebound when discontinuing long term treatment with corticosteroids.

Systemic effects due to topical corticosteroids are rare in adults, however, they can be severe. HPA suppression, hypercalcaemia, cataract, infections and increase in intra-

ocular pressure can occur, especially after long term treatment. Systemic effects occur more frequently when applied under occlusion, when applied on large areas or during long treatment.

Post Marketing Experience

Since events from post market use are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most frequently reported events are mentioned regardless of listedness.

Based on data from post market use Daivobet® gel on body and scalp psoriasis, the most frequently reported adverse events are exacerbation of psoriasis, pruritus, alopecia, burning sensation and erythema.

DOSAGE AND ADMINISTRATION

Daivobet® gel is FOR TOPICAL USE ONLY. Daivobet® gel is NOT FOR OPHTHALMIC USE.

The phototoxic effects of Daivobet® gel have not been studied in psoriasis patients in Australia. All psoriasis-affected areas treated with Daivobet® gel should be, where possible, protected from direct sunlight and UV-light with items of clothing.

Adults

Body psoriasis: Daivobet® gel should be applied once daily for up to 8 weeks.

If there is no response after 4 weeks, treatment should be ceased. Treatment of body psoriasis should be ceased after 8 weeks.

Scalp psoriasis: Daivobet® gel should be applied once daily for up to 4 weeks. After this period, Daivobet® gel may be used according to need under medical supervision. There is experience with intermittent courses of Daivobet® gel up to 52 weeks for scalp psoriasis.

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).

When using calcipotriol containing products, the maximum daily dose should not exceed 15 g and the maximum weekly dose should not exceed 100 g.

The total body surface area treated with calcipotriol **should not exceed** 30%. Repeated treatment of large body surface areas may result in adverse effects.

Shake the bottle before use.

In order to achieve optimal effect, it is recommended that the hair is not washed immediately after application of Daivobet® gel. Daivobet® gel should remain on the scalp during the night or during the day.

Children

Daivobet® gel is not recommended for use in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

OVERDOSAGE

Use at more than the recommended dose may cause elevated serum calcium, which rapidly subsides when treatment is discontinued.

Excessive prolonged use of topical corticosteroids may suppress the hypothalamic pituitary adrenal axis (HPA) resulting in secondary adrenal insufficiency, which is usually reversible. In such cases symptomatic treatment is indicated.

In case of chronic toxicity the topical corticosteroid treatment must be withdrawn gradually.

It has been reported that due to misuse one patient with extensive erythrodermic psoriasis treated with 240 g of Daivobet® ointment weekly (maximum dose 100 g weekly) for 5 months developed Cushing's syndrome and after abruptly stopping treatment developed pustular psoriasis.

Contact the Poisons Information Centre on 131 126 for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Daivobet® gel contains 50 micrograms calcipotriol per gram and 500 micrograms betamethasone (as dipropionate) per gram in an almost clear, colourless to slightly off-white gel. It is available in bottles of 30 and 60 g.

Storage: Store below 25°C. Do not refrigerate.

Keep the bottle in the outer carton in order to protect from light.

Shelf life: 2 years from date of manufacture

Use within 3 months of opening.

Do not use beyond the expiry date on the package.

Do not use if the pack shows signs of damage or tampering.

NAME AND ADDRESS OF SPONSOR

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And

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POISON SCHEDULE OF MEDICINE

S4

DATE OF APPROVAL

Initial Date of Approval: 14th July 2010

Date of most recent amendment: 22nd March 2013

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