Product Monograph

Spectro EczemaCare®
Medicated Cream
(Clobetasone Cream, B.P.)

Topical Corticosteroid

GlaxoSmithKline Consumer Healthcare Inc.
7333 Mississauga Road Mississauga,
OntarioL5N 6L4

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Product Monograph

Spectro® EczemaCare Medicated Cream

(Clobetasone Cream, B.P.)

THERAPEUTIC CLASSIFICATION

Topical corticosteroid

ACTIONS AND CLINICAL PHARMACOLOGY

Spectro EczemaCare Medicated Cream (0.05% clobetasone butyrate) is a moderately potent fluorinated topical corticosteroid. The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs which are effective when applied locally to control many types of inflammatory, allergic and pruritic dermatoses. Clobetasone butyrate has been shown to have topical and systemic pharmacologic and metabolic effects characteristic of the corticosteroid class of drugs. Topical corticosteroids such as clobetasone 17-butyrate are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, anti-pruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain.

Corticosteroids suppress inflammation by acting on multiple factors that are critical in generating the inflammatory responses. Corticosteroids are thought to induce a protein (lipocortin) that inhibits phopholipase A2, which results in decreased release of arachidonic acid and its derivatives (prostaglandins and leukotrienes). Due to decreased production of a number of

lipolytic and proteolytic enzymes, migration of leukocytes to the area of injury is inhibited. Similarly, corticosteroids inhibit adhesion of leukocytes to the vascular walls in the inflamed area by suppressing the activity of endothelial adhesion molecule-1 (ELAM-1) and intracellular adhesion molecule-1 (ICAM-1). Corticosteroids also act upon the host immune responses by suppressing the production and release of cytokines such as interleukins, interferon-gamma, and tumor necrosis factor-alpha. Although the biological effects by corticosteroids are not fully elucidated, the net effect of these multiple actions is the marked reduction of the inflammatory responses.

Indications and Clinical Use

Spectro EczemaCare Medicated Cream (clobetasone butyrate) is indicated in the treatment and control of small patches of eczema and dermatitis including atopic eczema and irritant and allergic contact dermatitis. To be applied to itchy, red, dry and inflamed skin to clear the flare-up and to break the itch-scratch cycle of eczema and dermatitis.

Contraindications

If no anti-infective agent is used simultaneously, clobetasone butyrate is not indicated for the treatment of primarily infected skin lesions caused by infection with fungi (e.g. Candidiasis, Tinea) or bacteria (e.g. Impetigo), primary cutaneous viral infections (i.e., herpes simplex, vaccinia and varicella), syphilitic skin infections or tuberculous skin lesions.

Clobetasone butyrate is contraindicated in patients with a hypersensitivity to any of the components of the preparation.

Clobetasone butyrate is also contraindicated in patients with acne vulgaris, rosacea, psoriasis, or pruritus without rash.

Warnings

If topical corticosteroids are used, over extensive areas, in large quantities, or on the face, scalp, axillae and scrotum, sufficient absorption may occur, giving rise to adrenal suppression and other systemic effects. Similarly absorption can be increased by the use of occlusion, which can lead to adrenal suppression especially in infants and children. The management of eczema and dermatitis in infants and young children requires the supervision of a physician. Treatment without the management of a physician is therefore limited to adults and children aged 12 years and over.

Use in children under 12 years only on the advice of a physician.
Use for no more than 7 days continuous treatment.

Patients are warned in product labelling against letting the cream get into the eye.

Patients are warned in product labelling not to use other topical corticosteroids, either prescribed or obtained over-the-counter (such as hydrocortisone), at the same time as Spectro EczemaCare Medicated Cream as this may increase the risk of unwanted effects.

Patients are warned in product labelling to use the minimum amount of cream for the shortest time necessary to relieve symptoms.

Patients are advised on product labelling to use on intact skin only.

Precautions

General

Spectro EczemaCare Medicated Cream should be used with caution in patients with stasis dermatitis and other skin diseases associated with impaired circulation.

If a symptomatic response is not noted within a few days to a week, the local application of Spectro EczemaCare Medicated Cream should be discontinued and the patient re-evaluated.

The safety and effectiveness of Spectro EczemaCare Medicated Cream when used under occlusive dressings has not been determined. Patients are advised on product labelling not to cover the treated skin with anything (plasters, dressing, gloves or cling film).

Although hypersensitivity reactions are rare with topically applied corticosteroids, the drug should be discontinued and appropriate therapy initiated if there are signs of hypersensitivity.

If irritation develops, Spectro EczemaCare Medicated Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis from corticosteroids, although uncommon, can be diagnosed by observing 'failure to heal' rather than clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

Patients are advised in product labelling to use Spectro EczemaCare Medicated Cream only for the treatment of eczema or dermatitis and not to use it on the groins, genitals, on axilla or

between the toes or on the face or scalp unless such use is conducted under medical supervision.

Patients are advised in product labelling that they should not use clobetasone butyrate for the treatment of psoriasis as there are no adequate studies that support the efficacy of clobetasone butyrate in the treatment of psoriasis.

Effect on Infection

In case of bacterial infections of the skin, appropriate anti-bacterial agents should be used as primary therapy. If it is considered necessary, the topical corticosteroid may be used as an adjunct to control inflammation, erythema and itching. If a symptomatic response is not noted within a few days to a week, the local application of corticosteroid should be discontinued until the infection is brought under control.

During the use of topical corticosteroids, secondary infections may occur. Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected. Any spread of infection requires withdrawal of topical corticosteroid therapy, and systemic administration of antimicrobial agents. Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressings, and so the skin should be cleansed before a fresh dressing is applied.

Systemic Effects

Significant systemic absorption may result when corticosteroids are applied over large areas of the body, used for prolonged periods or under occlusive dressings. To minimise this possibility, treatment should be interrupted periodically or one area of the body should be treated at a time

when long-term therapy is anticipated. In infants, the diaper may act as an occlusive dressing and increase absorption. Further, children may be more susceptible to systemic toxicity due to larger skin surface to body mass ratios.

Patients are advised in product labelling to inform subsequent physicians of the prior use of corticosteroids.

Patients are advised to tell their doctor or pharmacist before use if they are taking any prescription medication or over the counter products.

Drug Interaction

Co-administered drugs that can inhibit CYP34A (e.g. ritonavir, itraconazole) have been shown to inhibit the metabolism of corticosteroids leading to increased systemic exposure. The extent to which this interaction is clinically relevant depends on the dose and route of administration of the corticosteroids and the potency of the CYP34A inhibitor. Patients are advised on product labelling not to use with ritonavir or itraconazole.

Patients are advised on product labelling that some medicines may affect how Spectro EczemaCare Medicated Cream works, or make it more likely that the patient will experience side effects. These include: other corticosteroids medicines- these may include some eczema creams, ashma inhalers, tablets, injections, nasal sprays, and eye or nose drops.

Long Term Effects

Prolonged or extensive use of topical corticosteroid products may produce atrophy of the skin and subcutaneous tissue, particularly on flexor surfaces and on the face. If this is noted, the use of Spectro EczemaCare Medicated Cream should be discontinued.

Spectro EczemaCare Medicated Cream should be applied to the face only if in the estimation of a physician it is necessary and the benefits of application to the face outweigh the risks.

Pregnancy and Lactation

Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development. The relevance of this finding to human beings has not been established. However, the administration of clobetasone butyrate topical preparations during pregnancy and lactation should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Women, who are pregnant, may be pregnant, are planning to become pregnant or are breast feeding, are advised in product labelling not to use Spectro EczemaCare Medicated Cream without medical advice.

Drugs of this class should not be used extensively in pregnant patients in large amounts or for prolonged periods of time.

Use in Children

Spectro EczemaCare Medicated Cream is suitable for use in adults and children aged 12 years or older. Use in children under 12 years only on the advice of a physician.

Because of the higher ratio of skin surface area to body mass, children are at greater risk than adults for HPA axis suppression when treated with topical corticosteroids. They are also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's

syndrome while on treatment. Adverse effects including striae have been reported with use of topical corticosteroids in infants and children. HPA axis suppression and Cushing's syndrome have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include: linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACT stimulation.

In clinical practice, a substantial proportion of the use of Spectro EczemaCare Medicated Cream has been in children. There have been no published reports of significant untoward effects.

Use in Elderly

Clinical studies have not identified differences in responses between elderly and younger patients. The greater frequency of decreased hepatic or renal function in elderly may delay elimination if systemic absorption occurs. Therefore the minimum quantity should be used for the shortest duration of time to achieve the desired clinical benefit. All patients are advised on product labelling to use the minimum amount of cream for the shortest time necessary to relieve symptoms.

Use in Renal/Hepatic Impairment

In case of systemic absorption (when the application is over a large surface area for a prolonged period) metabolism and elimination may be delayed therefore increasing the risk of systemic toxicity. Therefore, the minimum quantity should be used for the shortest duration to achieve the desired clinical benefit. All patients are advised on product labelling to use the minimum amount of cream for the shortest time necessary to relieve symptoms.

Adverse Reactions

Side effects associated with short-term (up to 14 days) use include:

- Hypersensitivity
  - Local hypersensitivity reactions such as erythema, rash, pruritis, urticaria, local skin burning and allergic contact dermatitis may occur at the site of application and may resemble symptoms of the condition under treatment. In the unlikely event of signs of hypersensitivity appearing, application should stop immediately.
- Exacerbation of underlying symptoms may occur.

Local burning, irritation, itching, skin atrophy, dryness of the skin, atrophy of subcutaneous tissues, telangiectasia, striae, change in pigmentation, secondary infection and hypertrichosis have been observed following topical corticosteroid therapy.

If more than the correct amount of cream is used or if it is used for longer than recommended, the following symptoms may be experienced: increased weight, rounding of the face, obesity, skin thinning, or changes to the colour of skin and increased body hair.

Local atrophic changes could possibly occur in situations where moisture increases absorption of clobetasone butyrate, but only after prolonged use.

The following symptoms may occur with use in children: delayed weight gain, slow growth.

When large areas of the body are being treated with Spectro EczemaCare Medicated Cream (clobetasone butyrate) it is possible that some patients will absorb sufficient steroid to cause

transient adrenal suppression despite the low degree of systemic activity associated with clobetasone butyrate.

Other side effects may include: a decrease of the hormone cortisol in your blood, increased levels of sugar in your blood or urine, high blood pressure, cloudy lens in the eye (cataract), increased pressure in the eye (glaucoma), or weakening of the bones through gradual loss of mineral (osteoporosis).

Symptoms and Treatment of Overdosage

Acute overdosage is very unlikely to occur. Chronic overdosage requires continuous use of large quantities for long periods of time. In the case of chronic overdosage or misuse, the features of hypercortisolism may appear. As with any corticosteroid, treatment should be discontinued gradually if the symptoms of hypercortisolism appear. However, because of the risk of acute adrenal suppression in such cases, drug withdrawal should be carried out under medical supervision.

In case of overdose or swallowing, contact a health practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Dosage and Administration

See also INFORMATION FOR THE CONSUMER.

Spectro EczemaCare Medicated Cream is suitable for use in adults and children aged 12 years or older. Use in children under 12 years only on the advice of a physician.

Spectro EczemaCare Medicated Cream should be applied sparingly to the affected area twice a day for up to 7 days using fingertip units.

A single streak of cream from the top crease in the finger to the fingertip is one “fingertip unit”. This is enough to treat a patch area equal to the front and back of one hand. For smaller areas, squeeze out half a fingertip unit – enough to cover a patch of skin the same size as the palm of one hand.

If the condition resolves within 7 days, treatment with Spectro EczemaCare Medicated Cream should be stopped. If the condition does not improve in the first 7 days or becomes worse the patient is advised in product labelling to see a physician. If, after the recommended maximum duration of treatment, improvement is seen but further treatment is required, the patient is advised in product labelling to see a physician.

Under conditions of nonprescription use, the total dose of Spectro EczemaCare Medicated Cream applied should not exceed 15 grams per week in adults.

Pharmaceutical Information

Drug Substance

Proper Name: clobetasone butyrate (BANM, USAN, rINNM)

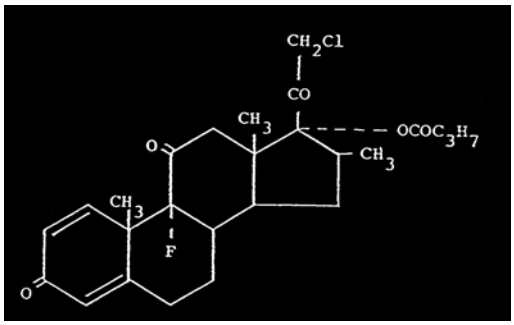
Chemical Name: 17 butyryloxy-21-chloro-9α-fluoro-16β-methyl-pregna-1,4-diene-3,11,20-trione

Molecular Formula: $C_{26}H_{32}ClFO_5$

Molecular Weight: 479

Description: white to cream colored crystalline powder

Solubility:



Clobetasone butyrate is insoluble in water, slightly soluble in ethanol, methanol and diethyl ether, soluble in dioxan and very soluble in toluene, chloroform, ethyl acetate, dimethysulphoxide and dimethylformamide

Melting Point: 178°C

Composition: Each gram of Spectro EczemaCare Medicated Cream contains 0.05% w/w clobetasone butyrate in a cream base.

Other ingredients are arlacel 165, beeswax substitute 6621, cetostearyl alcohol, chlorocresol, citric acid monohydrate, dimethicone 20, glycerin, glyceryl monostearate, purified water, sodium citrate dihydrate.

Storage Conditions: Store between 15-25°C.

Availability of Dosage Forms

Spectro EczemaCare Medicated Cream (clobetasone butyrate) is available in a 30 gram tube.

Information for the Consumer

Spectro EczemaCare Medicated Cream

Read all of this leaflet carefully.

You will find important information for you about the cream.

This cream is available without a doctor's prescription to treat eczema and dermatitis. It can help you to control patches of red, itchy, dry and inflamed skin caused by eczema and dermatitis. Follow the advice and instructions in this leaflet to make sure the cream is used properly.

Keep this leaflet. You may need to read it again.

Ask your pharmacist if you need more information or advice.

What is in Spectro EczemaCare Medicated Cream?

The active ingredient is clobetasone butyrate 0.05% w/w. This is a corticosteroid.

Other ingredients are arlacel 165, beeswax substitute 6621, cetostearyl alcohol, chlorocresol, citric acid monohydrate, dimethicone 20, glycerin, glyceryl monostearate, purified water, sodium citrate dihydrate.

1. How Spectro EczemaCare Medicated Cream works

Spectro EczemaCare Medicated Cream is one of a family of medicines called topical corticosteroids. *Topical* means it goes on the skin. *Corticosteroids* are used to control inflammation and itch. It helps control the inflammation that causes eczema or dermatitis. The

cream works to stop the skin's over-reaction to the triggers that cause skin flare-ups. The cream base has moisturising properties to help restore the skin barrier.

Topical corticosteroids are not the same as anabolic steroids – used illegally by some athletes and body builders – which are taken as tablets or injections. The two types of medicine are completely different. What we know about this cream comes from years of experience with it as a prescription treatment.

The cream comes in a 30 g tube. No more than 15 g should be used in a single 7 day period without consulting a doctor.

2. Do not use Spectro EczemaCare Medicated Cream

- **If you have ever had an allergic reaction** to clobetasone butyrate or to any of the other ingredients in the cream (See What is in Spectro EczemaCare Medicated Cream).
- **If you are pregnant, may be pregnant, are planning to become pregnant or breast feeding without first consulting a doctor.**
- **If you are using another corticosteroid.**

Do not use this cream (or any other corticosteroid) on the following skin problems: it could make them worse.

- **On infected skin:** like cold sores, herpes, chicken pox, impetigo, ringworm, athlete's foot or thrush. Corticosteroids do not cure infections caused by bacteria, yeast, viruses or fungi.

- On cuts and open wounds, to treat eczema around a leg ulcer, on itchy skin which is not red or inflamed, or on rosacea (a condition where the skin on the face is unusually red and small spots may develop), or on acne (spots or pimples).
- **On psoriasis:** Spectro EczemaCare Medicated Cream has not been shown to be effective in the treatment of psoriasis. This condition should be managed by a doctor.
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- **On seborrheic dermatitis:** This involves areas of skin where this cream should not be used
- Over large areas of skin.

If you have any other skin diseases, consult your doctor before using. Tell your doctor or pharmacist before use if you are taking any prescription medication or over the counter products.

Do not use other medications that contain corticosteroids, either prescribed or over-the-counter, as this may increase the risk of side effect . These medications may include some eczema creams, ashma inhalers, tablets, injections, nasal sprays, and eye or nose drops. Do not use Spectro EczemaCare Medicated Cream with ritonavir and itraconazole.

Do not use on children under 12

3. How to use Spectro EczemaCare Medicated Cream

Adults or children over 12 years

Use Spectro EczemaCare Medicated Cream on patches of red, itchy, dry and inflamed skin caused by eczema or dermatitis, for up to 7 days. If you're not sure what's causing your skin problem, ask your doctor.

Do not use the cream:

- On your face or scalp (but you can use it on the neck and ears)
- On the groin, genital area or armpits
- Between your toes

Do not use for more than 7 days and do not use more than 1/2 tube (15 g) in 7 days, except on the advice of a doctor.

Be especially careful that **you do not get the cream in your eyes**.

Use the cream twice a day, for up to 7 days

- Wash your hands and dry them
- Squeeze out the cream along the top of your index finger: see the picture
- A single streak of cream from the top crease in the finger to the fingertip is one "fingertip unit". This is enough to treat a patch area equal to the front and back of one hand. For smaller areas, squeeze out half a fingertip unit – enough to cover a patch of skin the same size as the palm of one hand. You only need a thin layer.
- Gently rub cream into the skin you are treating
- Wash your hands again (unless it is your hands you are treating).

- If you forget or miss a dose, use it when you remember.

Try to keep to the fingertip unit. Using steroids on the skin continuously over many weeks or months can cause skin thinning.

Do not cover the skin you treated with anything (plasters, dressings, gloves or cling film). It can cause more of the medicine to pass through the skin which can cause side effects. Use on intact skin only.

4. While using Spectro EczemaCare Medicated Cream

Spectro EczemaCare Medicated Cream is meant to control skin conditions that improve within 7 days of treating yourself. If you think you need further treatment after that, see a doctor for advice. Do not continue using it. The minimum amount of cream should be used for the shortest time necessary to relieve your symptoms.

If your skin condition clears up in less than 7 days, stop using Spectro EczemaCare Medicated Cream. You may use emollient (moisturising) products to help stop the condition from coming back. See the advice in section 7.

If your skin gets worse, or if it does not improve within 7 days, or if initially improves but then begins to get worse, **stop using Spectro EczemaCare Medicated Cream** and see your doctor. You may have a skin infection caused by bacteria, yeast or fungi (Spectro EczemaCare Medicated Cream does not cure these conditions), or a trigger you have not recognised, or even an allergy to the cream.

If your skin gets better but the redness or itching comes back within a short time, your skin may still be reacting to something that is touching it. Check the examples of **common triggers** in section 7.

5. Possible side effects

Local burning, itchiness, dryness of the skin have been observed. If these reactions persist contact your doctor.

Possible but rare reactions include skin atrophy (skin thinning), dryness of the skin, atrophy of subcutaneous tissues (thinning of tissues under the skin), telangiectasia (dilation of blood vessels), striae (stretch marks), and change in pigmentation (skin discolouration). However, this cream is unlikely to cause such problems as long as you follow the advice in this leaflet and do not apply it to your face or scalp, groins, genital areas, armpits or between your toes, and limit its use to small areas of the body for periods not longer than 7 days. If such reactions occur, contact your doctor. If you use more than the correct amount of cream or for longer than recommended you may experience: increased weight, rounding of the face, obesity, skin thinning or changes to the colour of your skin and increased body hair. Other side effects may include: a decrease in the hormone cortisol in your blood, increased levels of sugar in your blood or urine, high blood pressure, cloudy lens in the eye (cataract), increased pressure in the eye (glaucoma), or weakening of the bones through gradual loss of mineral (osteoporosis). Stop using and tell your doctor immediately if you experience any of the following: allergic reaction such as skin rashes, redness and itching. This is not a complete list of side effects. For any unexpected effects while using Spectro EczemaCare Medicated Cream, contact your doctor or pharmacist.

In case of overdose or swallowing, contact a health practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

6. Storing Spectro EczemaCare Medicated Cream

Keep this cream safely where children cannot see or reach it.

Store between 15-25ºC.

Do not use the cream after the expiry date on the tube end or carton. Dispose of it safely.

7. More about eczema and dermatitis

Skin specialists often advise people with eczema or dermatitis to use emollient (or moisturising) skin products, including creams and bath oils, to keep moisture in the skin. This can make your skin more resistant to flare-ups. Avoid using soap and heavily scented products. If you need to use a cleanser to remove dirt, oil, bacteria or make-up from your skin, dermatologists recommend a non-irritating gentle cleanser that does not contain dyes, fragrances or sodium based detergents. Ask your pharmacist for further information.

If a rash comes back

Sometimes people with dermatitis find their rash soon comes back after treatment, or never disappears completely. This is often because they are still in contact with their trigger: the thing that caused the reaction. If you cannot discover the reason, ask your doctor for advice.

These are common triggers

- Ear rings or studs (especially gold-plated ear rings)
- Other jewellery
- Coins
- Watch buckles, metal straps or the metal back of a watch

- Metal studs or fastenings on jeans, bras or underwear. All of these have a metal in them called nickel, which is a very common trigger. If you react badly to nickel, all of the triggers in the list could be a problem. So if you have reacted badly to gold-plated earrings, you will need to watch out for buckles, coins, jewellery and studs.

Other common triggers

Triggers include rubber and pine tree sap, which are used in all sorts of things we touch every day. You might find triggers:

- **In the home:** like household cleaning products, furniture polish, varnishes, rubber gloves or elastic in clothes
- **In substances you use at work:** like glues, oils, lubricants or cement
- **In the garden:** certain plants and weeds, gardening gloves.

Even if it is not practical to avoid triggers, there are often practical steps you can take – see the next section, *Finding out more*.

Finding out more

- Questions? Call 1-800-250-8866. Product Monograph available upon request.
- You may be able to find out more from the internet or public libraries.
- **If you have other questions** about Spectro EczemaCare Medicated Cream or are not sure about something, ask your doctor or pharmacist who will be able to advise you.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcare.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and :**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilence Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: ***Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

GSK Legal Line

Pharmacology

Pharmacological studies in man and animals have shown that clobetasone butyrate has a relatively high level of topical activity accompanied by a low level of systemic activity.

The anti-inflammatory properties of clobetasone butyrate reduce the erythema and itchiness associated with eczema and dermatitis.

When formulated as Spectro EczemaCare Medicated Cream, clobetasone butyrate, has little or no effect on hypothalamic-pituitary-adrenal function. This has been so even when Spectro EczemaCare Medicated Cream was applied to adults in large amounts under whole-body occlusion.

The cream base in Spectro EczemaCare Medicated Cream has long-lasting moisturising properties. Statistically significant 24 hour skin hydration with Spectro EczemaCare Medicated Cream has been demonstrated.

Pharmacokinetic Properties

A single application of 30 g clobetasone butyrate 0.05% ointment to eight patients (3 with eczema and 5 with psoriasis) resulted in a small rise in plasma clobetasone butyrate levels during the first three hours, not exceeding 0.6 ng/mL, then the levels gradually decreased. The maximum plasma level reached in the first three hours was 0.6 ng/mL. The rise in levels was followed by a more gradual decline with plasma levels of clobetasone butyrate falling below 0.1

ng/mL (the lower limit of the assay) after 72 hours. The normal diurnal variation in plasma cortisol levels was not affected by the application of clobetasone butyrate ointment.

Although pharmacokinetic studies were not carried out with the cream formulation, plasma clobetasone butyrate levels would be expected to be no greater, or even lower, with the cream formulation, as creams are less occlusive than ointments.

Toxicology

Acute Toxicity

The acute systemic toxicity of clobetasone butyrate was examined in a range of species and is summarized in the table below. LD50 values from acute studies with mice, rats, cats and dogs indicated the toxicity of clobetasone butyrate to be low.

After oral dosing, LD50 values were >1000mg/kg in mice and rats. One female mouse dosed with 4000mg/kg clobetasone butyrate died within 48hr, but all other animals survived the 7-day observation period and were apparently unaffected by treatment. No histological signs of specific toxicity were found in either mice or rats.

After parenteral dosing, LD50 values were >1000mg/kg in mice and rats, >37mg/kg in guinea pigs and rabbits, and >18mg/kg in cats and dogs. A detailed histological examination of mice body organs showed that the only effect attributable to clobetasone butyrate was the absence of thymus tissue.

Acute systemic toxicity of clobetasone butyrate

Species	Sex	Route of administration	LD50 (mg/kg)
Mouse	M,F	Po	>4000
Rat	M,F	Po	>1000
Mouse[1]	M,F	Sc	>3600
Rat	M,F	Sc	>1000
Guinea pig	M,F	Sc	>37
Rabbit	M,F	Sc	>38
Cat	M,F	Sc	>38
Dog	M,F	Sc	>18
Mouse[1]	M,F	Ip	~5000
Rat[1]	M	Ip	1510
Rat[1]	F	ip	1660

Notes:- (1) Tamura et al., (1980a).

Chronic Toxicity

Effects typical of those produced by glucocorticoids were detected in 1- and 6-month topical toxicity studies with a 0.05% (w/w) topical formulation of clobetasone butyrate, applied at a dose of 500mg/kg/day to the shaved skin of rats (Aii *et a*l., 1980). This is equivalent to a clobetasone butyrate dose of 0.25mg/kg/day. Another study lasting 1 month used a 0.5% (w/w) formulation of clobetasone butyrate (equivalent to 2.5mg/kg/day clobetasone butyrate). No significant differences from the control groups were observed in the animals treated for 1 month with 0.25mg/kg/day clobetasone butyrate. The animals in the 0.25mg/kg/day (6 months) and 2.5mg/kg/day (1 month) dose groups showed changes typical of corticosteroid administration, such as decreased body weight gain, leucopaenia and atrophy of the adrenals, thymus and spleen. Recovery was either complete or almost complete after one month.

In a 3-week subcutaneous toxicity study, groups of eight male and eight female rats were injected with either clobetasone butyrate (0.2, 1, 5 and 25mg/kg/day) or betamethasone alcohol

(0.12mg/kg/day). Two females in the high dose group died shortly before the end of the investigation; the cause of death could not be determined from histological examination. Most of the effects seen were typical of anti-inflammatory corticosteroid administration. The no-effect dose was determined to be 0.2mg/kg/day. At ≥1mg/kg/day clobetasone butyrate produced a decrease in body weight gain. Hematological changes included a depression of mononuclear cell count, and, at three weeks, an increase in neutrophils. Post mortem findings included: a decrease in heart, lung, liver, kidney and gonad weight, a marked decrease in thymus and adrenal weight, and smaller decreases in prostate and uterus weight. Histological findings included thymic involution, fatty replacement of bone marrow, atrophy of the inner adrenal cortex, and a decrease or disappearance of endometrium eosinophils. These changes were generally dose-related, with 0.12mg/kg/day betamethasone producing effects comparable to those obtained with 5-25mg/kg clobetasone butyrate.

In a 1-month subcutaneous toxicity study by Tamura *et a*l. (1980a), groups of 10 male and 10 female rats received injections of 0.01, 0.03, 0.1, 1.0, 10 or 100mg/kg/day clobetasone butyrate for 6 days/week. Further groups comprising five rats of each sex received 0.1 or 10mg/kg/day clobetasone butyrate, and were then allowed to recover for 31 or 60 days after the end of the dosing period. The no-effect dose was determined to be 0.03mg/kg/day. Dose-related effects, typical of anti-inflammatory corticosteroid treatment, in rats given ≥0.1mg/kg/day included: decreased body weight gain, emaciation, atrophy of the inner adrenal cortex, lymphatic and hemopoietic tissues, lymphopaenia and an increase in serum cholesterol. Treatment-related effects in rats given ≤1mg/kgday were generally reversible. Irreversible changes (which may not be treatment-related) included a ‘fatty infiltration’ of pancreatic exocrine glands in males dosed with ≥1mg/kg/day, and females dosed with ≥10mg/kg/day.

In a 12-week subcutaneous study, five dose groups comprising 10 male and 10 female rats received 0, 0.2, 0.8, 3.2 or 12.8mg/kg/day clobetasone butyrate. A further group received 0.1mg/kg/day betamethasone alcohol. Systemic effects typical of anti-inflammatory administration were observed. All animals from the two highest dose groups, except one male, died before the end of the dosing period. They all showed signs of local inflammation; in addition, multiple pelvic abscesses were histologically confirmed in one rat. Histopathological investigation of the animals from the two high dose groups attributed the lesions to infection toxaemia in immunologically-suppressed animals. Two rats died in the 0.2mg/kg/day group (one male and one female after 12 and 28 doses, respectively), with pyelonephritis and subcutaneous abscess. Doses of $\leq$0.8mg/kg/day resulted in reduced growth, thymic involution and adrenal cortical atrophy, with animals in the 0.8mg/kg/day group also developing hypoglycaemia and increased levels of aspartate transaminase and alkaline phosphatase. The above mentioned changes were also observed with betamethasone-treated rats, with the severity of lesions equivalent to those seen in the 0.8mg/kg/day clobetasone butyrate group.

Tamura *et a*l. (1980b) reported on a 6-month subcutaneous toxicity study of clobetasone butyrate. Groups of five male and five female rats received sc injections of 0, 0.003, 0.01, 0.03, 0.1 or 0.3mg clobetasone butyrate/kg/day for 6 months. Doses of up to 0.03mg/kg/day induced no significant treatment-related effects. Higher doses of 0.1 and 0.3mg/kg/day induced some suppression of body weight gain, emaciation, atrophy of the adrenal, lymphatic and hemopoietic tissues, and lymphopaenia; these changes were reversible, with no significant differences between treated and control animals apparent two months after the end of the dosing period.

The intramuscular toxicity of clobetasone butyrate (0, 0.2, 0.7, 2.5 or 8.6mg/kg/day) was investigated using five groups of two male and two female Beagle dogs in a 13-week study.

Three dogs from the high dose group died before the end of the dosing period. These animals had swollen or sore limbs, and/or blood in their faeces. Histological examination revealed a variety of changes, with pathogens isolated from the subcutaneous abscesses of two dogs. The other dogs survived the dosing period, and appeared healthy. Effects typical of anti-inflammatory corticosteroid administration were produced in dogs treated with ≥0.7mg/kg/day clobetasone butyrate.

Reproductive Toxicity Studies

Administration of corticosteroids to pregnant animals can cause abnormalities of fetal development. A high incidence of cleft palate in fetuses of laboratory animals is a well-described and common finding following corticosteroid treatment.

The teratogenic effects of clobetasone butyrate were assessed in the mouse, rat and rabbit. The proportion of fetuses with skeletal immaturity and cleft palate increased with clobetasone butyrate administration.

Fertility Studies

No company data regarding the effects of clobetasone butyrate on fertility in laboratory animals have been generated, and no published data could be found.

Organogenesis Studies

Pregnant mice were subcutaneously injected with clobetasone butyrate at doses of 1, 3, 10 or 30mg/kg/day from Days 7-16 of pregnancy. The animals were killed on Day 19 and their uterine contents examined. Clobetasone butyrate treatment had no effect on the number of implantation

sites or sex ratio. However, at doses of ≥3mg/kg/day, an increase in the number of dead fetuses and resorption sites was noted. A dose-related increase in the number of mice with cleft palate or skeletal immaturity was also observed. The incidence of cleft palate was 0.7% for untreated mice, 1.9% for the 1mg/kg/day dose group, and 95% in the 10mg/kg/day dose group.

A small number of soft tissue abnormalities were also evident in the dead fetuses from the high dose group.

A rat organogenesis study using topical application has been reported by Aii *et a*l. (1980). From Days 7-17 of pregnancy, 0.2g of an ointment formulation containing either 0.05% or 0.5% clobetasone butyrate was applied daily to the shaved skin of rats (equivalent to a clobetasone butyrate dose of 0.5mg/kg/day and 5mg/kg/day, respectively, using a female rat body weight of 200g). Treatment was associated with a small increase in the number of skeletal abnormalities, which were more prominent in the 0.5% dose group. The 0.5% formulation caused impaired weight gain, and reduced thymus, adrenal and spleen weight. Parturition and ossification were unaffected, and no teratogenic effects were observed. The authors noted that in spite of the fetal effects, the offspring in both dose groups grew normally, with normal neurological test results at 4 weeks of age.

In a study in Dutch rabbits, groups of 10 animals were subcutaneously injected with clobetasone butyrate at doses of 10, 30, 100 or 300mg/kg/day from Days 6-18 of pregnancy. A further group received 100mg betamethasone alcohol/kg/day. The animals were killed on Day 19 of pregnancy and their uterine contents examined. The 10mg/kg/day dose was determined to be the no-effect dose. Clobetasone butyrate at doses of up to 100mg/kg/day had no effect on implantation, the number of live fetuses, resorptions or live litter weight. At doses ≥30mg/kg/day,

a dose-related incidence of cleft palate occurred; other abnormalities affecting the skull, fore and hind limbs were noted, mainly in the two high dose groups. A delay in the maturity of fetuses from the two highest clobetasone butyrate dose groups and the betamethasone group was observed. The 300mg/kg/day clobetasone butyrate dose group exhibited results equivalent to the 100mg/kg/day betamethasone animals, with a reduction of body weight during the second half of pregnancy, marked reductions in the number and weight of live fetuses, and an increase in the number of resorption sites.

Peri- and Post-Natal Development

No company data regarding the peri/post-natal development of clobetasone butyrate treated laboratory animals have been generated, and no published data could be found.

Genotoxicity Studies

Clobetasone butyrate showed no evidence of mutagenic activity in studies with *Salmonella typhimurium* and *E. coli* at concentrations of up to 1000mg/plate, with and without metabolic activation using rat liver S9 fraction.

Clobetasone butyrate did not induce detectable increases in gene conversion frequencies at test concentrations of 100, 300 and 1000mg/mL in the yeast gene conversion assay with *Saccharomyces cerevisiae* JD1.

Clobetasone butyrate did not demonstrate mutagenic potential in the *in vitro* mouse lymphoma assay.

Clobetasone butyrate was screened for its potential to induce chromosome damage *in vitro* using cultured human lymphocytes, and *in vivo* in two rat micronucleus tests: Clobetasone butyrate was not clastogenic in human peripheral lymphocytes. The cells were treated with concentrations of up to 90mg/mL for 24hr in the absence of S9-mix, and 400mg/mL for 1hr in the presence of S9-mix.

In the first micronucleus test, marginal (but statistically significant) increases in the incidence of micronuclei were observed in the bone marrow of rats killed at 48hr after sc administration of 100, 300 and 1000mg/kg clobetasone butyrate. The effects were not dose-related and increases in micronuclei were not observed 24hr post-dose. The lack of dose response contrasts with the increasing plasma concentrations of drug obtained with increasing dose.

A repeat micronucleus test in which animals received single sc doses of 10 or 100mg/kg, showed an increase in micronuclei incidence, but only 48hr after treatment with the highest dose.

The mean increases in micronuclei observed in both studies were extremely small, and there was considerable inter-animal variation in response. For example, in the second study a control range between 0 and 4 micronucleated cells per 1000 immature erythrocytes was obtained, whilst the range for animals treated with 100mg/kg clobetasone butyrate fell between 1 and 6. Consequently in this group, the micronucleus incidence for only 2 animals fell outside the control range. In the light of these observations, it is concluded that the small increases in micronuclei observed in rat bone marrow are unrelated to any genotoxic effect of this drug. The effects could be the consequence of a generalized action of this drug on cell homeostasis within

the bone marrow for individual animals. In conclusion, the administration of clobetasone butyrate is not considered to pose a clastogenic risk to exposed individuals.

Carcinogenicity Studies

Carcinogenicity studies have not been performed with clobetasone butyrate. There was no requirement for such studies when the compound entered clinical use. Preclinical studies, and more importantly extensive clinical experience, do not suggest a carcinogenic risk for clobetasone butyrate.

Other Hormonal Activities

Clobetasone butyrate (1mg/animal) did not demonstrate significant mineralcorticoid activity after subcutaneous administration to adrenalectomised rats. It had no effect on sodium excretion or urine volume, but did increase potassium excretion, an effect attributable to its glucocorticoid activity.

Subcutaneous clobetasone butyrate was devoid of anabolic and androgenic effects in mice and rats. In female mice, 1.6mg clobetasone butyrate was without effect on kidney and preputial gland weight. In male mice, 2mg clobetasone butyrate was without effect on seminal vesicle weight, although a significant reduction in the growth rate and levator ani weights was noted.

Clobetasone butyrate (0.5mg/animal) showed no estrogenic activity in either mice or rats, as no significant increase in uterine weight was observed. In mice, 0.5mg clobetasone butyrate, when administered concomitantly with 0.1mg estrogen, inhibited the uterine growth produced by estrogen alone, demonstrating a significant anti-estrogenic effect. This effect was confirmed in

the rat where subcutaneous clobetasone butyrate had approximately 8% of the anti-estrogenic activity of subcutaneous progesterone; by the oral route, clobetasone butyrate had 2.5% of the activity of subcutaneous progesterone.

In the rabbit, subcutaneous clobetasone butyrate (0.2, 0.4 and 0.8mg/animal) demonstrated approximately three times the progestational activity of subcutaneous progesterone (0.4, 0.8 and 1.6mg/animal), as determined by increased uterine carbonic anhydrase levels.

Clobetasone butyrate was devoid of anti-gonadotrophic activity, as determined by testicular weight, when administered subcutaneously to male rats.

The effect of subcutaneous clobetasone butyrate, at doses of up to 18mg/animal, on hypothalamic-pituitary-adrenal function was approximately 5% that of betamethasone alcohol in stressed male mice.

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