

**calcipotriol and betamethasone dipropionate, 50 micrograms/g +
500 microgram/g gel (Xamiol®) No. (559/09)**

LEO Pharma

10 July 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

calcipotriol and betamethasone dipropionate scalp gel, (Xamiol®) is accepted for use within NHS Scotland for the topical treatment of scalp psoriasis.

Short-term comparisons have shown that the combination is more effective than either component used as monotherapy.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

<p>Indication</p> <p>The topical treatment of scalp psoriasis.</p>
<p>Dosing information</p> <p>The gel should be applied to affected areas of the scalp once daily. The recommended treatment period is 4 weeks. After this period repeated treatment with the gel can be initiated under medical supervision.</p> <p>All the affected scalp areas may be treated with the gel. Usually an amount between 1g and 4g per day is sufficient for treatment of the scalp.</p> <p>When using calcipotriol containing products, the maximum daily dose should not exceed 15g and the maximum weekly dose should not exceed 100g. The body surface area treated with calcipotriol containing products should not exceed 30%.</p>
<p>Product availability date</p> <p>04 November 2008</p>

Summary of evidence on comparative efficacy

Calcipotriol is a vitamin D analogue which is believed to induce differentiation and suppress proliferation of keratinocytes, forming the basis for its effect in psoriasis. As a topical steroid, betamethasone dipropionate has anti-inflammatory, antipruritic, vasoconstrictive and immunosuppressive properties.

Evidence for the efficacy of calcipotriol and betamethasone dipropionate gel in the treatment of scalp psoriasis came from two pivotal randomised, double-blind, 8-week clinical studies. They were of very similar design, enrolling patients with scalp psoriasis involving greater than 10% of the total scalp area, assessed as of at least moderate severity and with a history of psoriasis vulgaris of the body. There was a 2-week to 6-month washout period, as necessary. Comparators were betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle (both at the same concentration as in the combination product) and also, in the first study only, the gel vehicle; all were used once daily. Assessments were made at baseline and after 1, 2, 4, 6 and 8 weeks and consisted of: an Investigator's Global Assessment (IGA) of disease severity, a 6-point scale ranging from absence of disease to severe disease; clinical signs of scalp psoriasis (redness, thickness and scaliness, each scored on a 5-point scale); extent of scalp psoriasis (a 6-point scale) and patient's overall assessment of treatment (a 7-point scale). In both studies, the primary response criterion was the proportion of patients with absent or very mild "controlled disease" according to the IGA at week 8; the other assessments formed the basis of secondary end-points, as did the presence of controlled disease according to the IGA at weeks 2 and 4. The primary response criterion was analysed based on the full analysis set, using the last observation carried forward method, and was compared between the treatment groups using the Cochran-Mantel-Haenszel test adjusting for the effect of centre.

In the first study, patients were randomised in a 4:4:2:1 ratio to receive either the combination product (541 patients), betamethasone in the gel vehicle (556 patients), calcipotriol in the gel vehicle (272 patients) or the gel vehicle alone (136 patients).

At week 8, controlled disease was achieved by 71% of patients receiving the combination product, 64% in the betamethasone group, 37% of those receiving calcipotriol and 23% of those receiving the vehicle alone. The combination product was significantly more effective than betamethasone (odds ratio (OR) 1.41; 95% confidence interval (CI) 1.08 to 1.83), calcipotriol (OR 4.13; 95% CI 3.00 to 5.70) and the vehicle alone (OR 8.65; 95% CI 5.52 to 13.56). All other efficacy parameters supported these results. A key secondary end-point taken from the study was the proportion of patients with controlled disease according to the IGA at 4 weeks. This was noted in 67% of those receiving the combination product, 55% of those receiving betamethasone, 24% of the calcipotriol group and 15% of those receiving the vehicle only. The combination product was significantly more effective than all the others (at a significance level of 0.7%), with an OR of 1.72 when compared with betamethasone, 6.59 when compared with calcipotriol and 11.82 when compared with the gel vehicle.

In the second study, patients were randomised 2:2:1 to receive either, the combination product (568 patients), betamethasone in the gel vehicle (563 patients), or calcipotriol (286 patients). At week 8 controlled disease was achieved by 68% in the combination group, 61% in the betamethasone group and 43% of those receiving calcipotriol. The combination product was significantly more effective than betamethasone (OR 1.41; 95% CI 1.09 to 1.81) and calcipotriol (OR 3.13; 95% CI 2.29 to 4.28). Again, the other assessments supported these results. The proportion of patients with controlled disease at 4 weeks was 55% of those receiving the combination product, 51% of those receiving betamethasone and 26% of those receiving calcipotriol. The combination product was only significantly more effective than the calcipotriol product (OR 3.87).

Summary of evidence on comparative safety

No new safety issues were raised.

The frequency of adverse events (AE) across the studies was similar between the combination product and the betamethasone in gel vehicle and lower than the calcipotriol in gel vehicle. Most were mild to moderate in severity. There was a low incidence of adverse reactions around the treatment area.

A long-term (52 week) safety study was conducted, comparing the combination product with calcipotriol in gel vehicle, although the treatments were used on an as needed basis, and thus not at the licensed dose. Patients were randomised in a 1:1 ratio to receive either the combination product (419 patients) or calcipotriol (431 patients). There was a significantly lower rate of adverse reactions in the combination group (17%) compared with the calcipotriol in gel vehicle group (30%). The incidence of common adverse reactions (reported by $\geq 2.0\%$ patients) was similar for the two treatment groups with the exception of pruritus and skin irritation, which were more frequently reported in the calcipotriol in gel vehicle group. Adverse events associated with long-term corticosteroid use were not observed with the combination gel. The percentage of patients reporting lesional/perilesional AEs on the scalp was significantly lower in the combination group (12%) compared with the calcipotriol in gel vehicle group (22%). Serious AEs were reported in 19 patients receiving the combination product and 22 patients receiving calcipotriol; all were considered unrelated to study treatment, except one case of sinus tachycardia with calcipotriol, which was considered possibly related.

Summary of clinical effectiveness issues

This combination of active ingredients, which is already widely available and used in a product for application to the body, has now been formulated in a gel vehicle for ease of use on the scalp. Once-daily application may offer patient benefits; at present this combination has to be administered as two separate products, one of which is used twice daily. Whilst use of a fixed combination may limit the flexibility of dosage of the individual constituents, product acceptability is a major obstacle to compliance in this field and this new formulation offers both an acceptable formulation and simplicity of use.

The most robust data from the studies is that of efficacy and safety at 8 weeks; however the recommended treatment period is 4 weeks. A long-term safety study (1 year) did not reflect the licensed dose as the gel was applied on an 'as needed' basis and thus the data are less relevant.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis, using a one-year Markov model, to compare calcipotriol and betamethasone dipropionate combination gel with standard care for the treatment of moderate severity scalp psoriasis. The model assumed all patients had failed on emollients or coal tar shampoos. The model included a selection of twelve comparator pathways, each of three lines. Seven of these pathways contained the combination gel as a first, second, or third-line agent. The benchmark pathway was betamethasone valerate, calcipotriol then calcipotriol plus betamethasone dipropionate administered as separate products.

The clinical effectiveness measure was controlled disease at four weeks. The estimated response rates for each treatment were calculated from a mix of indirect comparison, meta analysis, direct comparison and GP opinion. The costs of drugs, using volumes as observed in the clinical studies, with follow-up in primary care and out-patients where necessary, were included. The utility values were derived from SF-36 scores, a health related quality of life measure, recorded in one of the clinical studies.

Using the combination gel as first-line, compared to the mean costs and utilities calculated for five standard care pathways, resulted in a cost per QALY of £12,643. This was based on an incremental cost of £32.40 and a gain in QALYs of 0.00256.

The reported incremental cost effectiveness ratio was not sensitive to positioning the gel as first, second or third-line. The results were sensitive to the comparator pathway, utility values, relapse rates, cost of day clinic management, drug costs and the volumes applied. For example, comparing the combination gel first-line to the benchmark pathway resulted in a cost/QALY of £34,371. The results for use as second and third-line compared to the benchmark pathway were £40,951 and £31,701 respectively. Increasing the 4-week relapse rate (common across all treatments) from 20% to 30% increased the cost per QALY to £21,240, whilst on a 'use as need' basis the gel was dominant over comparators.

The main concerns with the parameter values assumed were:

- a) The volume of gel used in the clinical studies was 68g; the model assumed two tubes of 60g each would be prescribed. In practice only one tube is likely to be prescribed, halving the drug costs and therefore improving the cost-effectiveness of the treatment.

- b) The incremental gain in utility value for a responder compared to a non-responder was assumed to be 0.0181. This is very small and not consistent with the values in the literature. The gain was derived from SF-36 scores and measured in one of the clinical studies. It may be this tool was not sensitive to the attributes of the disease.
- c) The clinical efficacy assumed for certain comparator medicines. The response rates have been derived by indirect comparison of heterogeneous studies and it was unclear whether meta-regression methods were used to adjust for differences in studies. The results may therefore have understated the response rates of some of the comparators. However, further sensitivity analyses have been provided to reduce this concern.

Despite some limitations with the analysis, the economic case was considered to be demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- PSALV
- Skin Care Campaign Scotland

Additional information: guidelines and protocols

The American Academy of Dermatology is currently publishing a series of guidelines for the management of psoriasis and psoriatic arthritis. Part 3 of the series was published in February 2009 and relates to the use of topical therapies. There is no specific discussion of the treatment of scalp psoriasis.

Additional information: comparators

Other therapies for the treatment of scalp psoriasis include the vitamin D analogue alone, steroid preparations, dithranol creams as short contact therapy and coal tar products.

Cost of relevant comparators

Drug	Formulation	Dose regimen	Unit cost (£)	Cost per 100gram or 100ml (£)
calcipotriol with betamethasone dipropionate	scalp gel; 50 microgram/g and 0.05%	1 to 4g once daily	60g = 35	58
dithranol	cream; 0.1% to 3%	0.1% to 0.5%, overnight treatment; 1% to 3%, up to 1 hour only	50g = 4 to 17	8 to 34
calcipotriol	scalp solution; 50microgram/ml	twice daily (max 60ml weekly)	120ml = 25	21
fluocinolone acetonide	gel; 0.025%	one to two times daily	60ml = 10	17
mometasone furoate	scalp lotion; 0.1%	once daily	30ml = 4	15

betamethasone dipropionate with salicylic acid	scalp application; 0.05% and 2%	once to twice daily	100ml = 10	10
hydrocortisone butyrate	scalp lotion, 0.1%	once to twice daily	100ml = 10	10
coal tar	scalp ointment; coal tar solution 12%, salicylic acid 2%, precipitated sulphur 4%	as necessary	100g = 9	9
betamethasone dipropionate	lotion, 0.5%	up to twice daily	30ml = 3	8
betamethasone valerate	scalp application; 0.1%	once to twice daily	100ml = 4	4

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 07 May 2009 and MIMS (May 2009). Relative costs will vary according to the amount of product used, which in turn will depend on the size of area to be treated, the number of daily applications and treatment duration.

Additional information: budget impact

The net and gross drug costs were presented for two scenarios; both assume 2,511 patients are treated in year 1 and 10,902 in year 5. The first scenario was based on treatment usage consistent with current Scottish prescribing approaches. This forecast gross costs in year 1 of £274.9k rising to £1.19m in year 5. The net costs, calculated by deducting the savings from the other treatments, were £225.8k and £1.01m respectively.

The second scenario used the volumes of drugs observed in the clinical studies. This forecast gross costs in year 1 of £549.9k rising to £2.39m in year 5. The net costs were £461.2k and £2.07m respectively.

The manufacturer noted the former is likely to be the more accurate forecast.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 11 June 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Jemec GBE, Ganslandt C, Ortonne JP et al. A new scalp formulation of calcipotriene plus betamethasone compared with its active ingredients and the vehicle in the treatment of scalp psoriasis: A randomised, double-blind, controlled trial. *J Am Acad Dermatol* 2008;59:455-63.

Van de Kerkhof P, Hoffmann V, Anstey A et al. A new scalp formulation of calcipotriene plus betamethasone in the treatment of scalp psoriasis compared to its active ingredients in the same vehicle. *British Journal of Dermatology* 2009;160:170-6