tacrolimus 0.1% ointment (Protopic®) No. (609/10)
Astellas Pharma Ltd

05 March 2010

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

tacrolimus 0.1% ointment (Protopic®) is accepted for restricted use within NHS Scotland.

Licensed indication under review: the maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in adult patients (≥16 years) experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

SMC Restriction: Use is restricted to initiation by doctors with a specialist interest and experience in treating atopic dermatitis using immunomodulatory therapy (this can include General Practitioners).

Twice weekly maintenance therapy with tacrolimus ointment resulted in reduced disease exacerbations when compared to intermittent use only to treat disease exacerbations.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For maintenance treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in adult patients (≥16 years) experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

Tacrolimus ointment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

Dosing information

Patients who are responding to up to 6 weeks treatment using tacrolimus ointment twice daily (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment which should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2 to 3 days without treatment. Adult patients (≥16 years) should use tacrolimus 0.1% ointment. If signs of a flare reoccur, twice daily treatment should be re-initiated.

After 12 months, a review of the patient`s condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

Product availability date

3 June 2009

Summary of evidence on comparative efficacy

Atopic dermatitis, synonymous with atopic eczema, is a common inflammatory skin disease characterised by intense itching, dry skin, redness, inflammation and exudation. It typically follows a chronic course of flares and remissions. Tacrolimus is a calcineurin inhibitor which acts as an immunosuppressant mainly reducing inflammation by suppressing the T-cell response. Tacrolimus ointment (0.1% and 0.03%) is licensed for twice daily application for the treatment of moderate to severe atopic dermatitis in adults (≥16 years) who are not adequately responsive to, or are intolerant of, conventional therapies such as topical corticosteroids. The submission represents an extension of this licence to include twice weekly application of 0.1% ointment as maintenance treatment in adult patients, with a high frequency of disease exacerbations (i.e. more than four per year), who have had an initial response to a maximum of 6 weeks of treatment with tacrolimus ointment applied twice daily.

There is one pivotal study to support the efficacy of tacrolimus ointment for maintenance in adult patients. This study enrolled patients with active, mild to severe atopic dermatitis who entered an open-label period during which affected lesions were treated with tacrolimus 0.1% ointment twice daily for 8 days to 6 weeks until improvement of disease had reached an Investigator's Global Assessment (IGA) ≤ 2, (i.e. clear, almost clear or mild disease). Patients not achieving an IGA of ≤ 2 were withdrawn from the study. Thereafter, patients were randomised in a ratio of 1:1 to tacrolimus 0.1% or vehicle twice weekly for a 12-month disease control period. Randomisation was stratified by centre and disease severity.

If a disease exacerbation occurred in the tacrolimus or vehicle group, patients were treated with open-label tacrolimus ointment twice daily for up to 6 weeks until the IGA score of ≤ 2 was regained before returning to the original blinded randomised treatment.

The primary endpoint was number of disease exacerbations during the disease control period requiring substantial therapeutic intervention (defined by an IGA of 3 to 5 [i.e. moderate, severe or very severe] measured on day 1 of the exacerbation and requiring > 7 days treatment with tacrolimus) in the full analysis set (all randomised patients who applied the study medication at least once or had at least one post baseline value). Secondary endpoints included the total number of disease exacerbations, the percentage of days of disease exacerbation treatment and the time to first disease exacerbation. The IGA, the Eczema Area and Severity Index (EASI) and modified EASI (mEASI) were used to assess clinical improvement and quality of life was measured using the Dermatology Life Quality Index (DLQI). The last-observation-carried forward (LOCF) methodology was used to account for missing data.

Two hundred and fifty-seven patients were enrolled in the open-label phase of whom 116 were randomised to tacrolimus 0.1% and 108 to vehicle ointment twice weekly. The median number of disease exacerbations requiring substantial therapeutic intervention was significantly lower in the tacrolimus group than the vehicle group (0.0 versus 3.0 respectively). Fifty-seven percent (66/116) tacrolimus and 30% (32/108) vehicle treated patients experienced no exacerbations requiring a substantial therapeutic intervention. Subgroup analysis in patients with moderate and severe disease (the licensed population) found that the median number of disease exacerbations requiring a substantial therapeutic intervention was 1.0 (n=80) and 5.3 (n=73) respectively and that 49% (39/80) and 18% (13/73) of patients respectively experienced no disease exacerbation requiring a substantial therapeutic intervention confirming a significant between-group difference.

Secondary endpoints also significantly favoured tacrolimus 0.1% ointment twice weekly over vehicle during the disease control period. In addition, subgroup analyses demonstrated that post-baseline values for secondary endpoints consistently favoured tacrolimus over vehicle in the moderate to severe atopic dermatitis subgroup. The differences were significant for key secondary endpoints relating to disease exacerbations in the moderate and severe subgroup.

Summary of evidence on comparative safety

During the pivotal study, there were no new reported adverse events that had not been previously reported with tacrolimus ointment. In the licensed moderate to severe atopic dermatitis subgroup, treatment-related application-site infection was more common in the tacrolimus maintenance group (6.3% versus 2.7%).

Summary of clinical effectiveness issues

The study compares the use of tacrolimus as a proactive twice weekly maintenance therapy with intermittent reactive therapy to treat exacerbations of atopic dermatitis. The results demonstrated that maintenance therapy with tacrolimus significantly reduced the number of disease exacerbations compared with intermittent reactive therapy, regardless of the severity of disease at baseline.

The study enrolled patients with mild to severe atopic dermatitis however tacrolimus ointment is only licensed for patients with moderate or severe disease. Although subgroup

analysis in the moderate to severe subset confirmed that the results for the primary endpoint were consistent with the entire study population, the study was not designed to test the significance in subgroups.

The open-label period of the study aimed to allow stabilisation of disease before randomisation but this may have biased the results towards patients who were responsive to tacrolimus treatment as only controlled patients were eligible for randomisation. However the licence indicates that it is patients who are responding to initial treatment with tacrolimus ointment twice daily who are suitable for maintenance therapy.

In practice, tacrolimus maintenance therapy will only be used in patients who have had an initial response to twice daily tacrolimus for flares. The licence for intermittent reactive therapy requires patients to be inadequately responsive to, or intolerant of, conventional therapies such as topical corticosteroids. This was not an entry criterion for the study and the proportion of patients who were unresponsive to, or intolerant of, conventional therapies is unknown.

During the disease control period, there was wide variation in the amount of tacrolimus ointment used in patients in both groups making it difficult to compare the relative quantities of ointment used in a maintenance or intermittent strategy. It is therefore not clear whether using maintenance therapy resulted in less overall use of tacrolimus than intermittent therapy.

The study used LOCF methodology to account for missing data. However, given the relatively high discontinuation rates during the disease control period (35 patients, 30.2% in the tacrolimus arm and 53 patients, 49.1% in the vehicle arm) and the relapsing/remitted nature of atopic dermatitis, this may have biased the results.

Cases of lymphoma and skin malignancy have been reported in patients using tacrolimus ointment. Although studies conducted with intermittent therapy for up to 4 years have not shown evidence for development of lymphoma, a recent cohort study has suggested an increased risk of T-cell lymphoma with tacrolimus ointment. The safety of maintenance therapy with topical tacrolimus is currently limited to 12 months and the SPC states that after 12 months, a review of the patient`s condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing tacrolimus maintenance treatment with tacrolimus reactive treatment in adult patients with moderate to severe atopic dermatitis experiencing a high frequency of disease exacerbations and who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment. The manufacturer stated that, in line with previous SMC guidance for the use of tacrolimus for reactive treatment, maintenance treatment is limited to patients who are not adequately responsive to, or are intolerant of, conventional therapies such as topical corticosteroids.

Clinical data were taken from the subgroups reflecting the licensed indication in the pivotal study and were used to model the costs and benefits of treatment over a one-year time horizon. Utility values used in the model were taken from the literature and were also used by NICE in a previous HTA of atopic dermatitis treatments.

Resource use estimates were based on clinical opinion and were largely related to the subsequent treatment of patients who discontinue tacrolimus and receive further treatments such as phototherapy and oral steroids.

In the base case analysis the manufacturer estimated that tacrolimus maintenance treatment would dominate tacrolimus reactive treatment i.e. would be more effective and would result in savings of £623 in patients with moderate disease and £1,560 in patients with severe disease with estimated QALY gains of 0.01 and 0.09 respectively. When the treatment of discontinuations was excluded from the model the incremental cost-effectiveness ratio (ICER) increased to £10,558 per QALY for the moderate subgroup but was still dominant in the severe subgroup.

There were some limitations with the analysis:

- Data on the primary outcome measure were not used directly in the model. Instead, the data used in the model from the pivotal trial included the days in a disease exacerbation, ointment usage per day, the number of tacrolimus treatment days and the discontinuation rates. While these were based on secondary outcome measures and thus may not be powered to detect significant differences, the analysis seemed reasonable.
- It was assumed that all subsequent therapies (such as phototherapy, oral steroids and topical steroids) are equally effective but sensitivity analysis on this assumption indicated that the results were fairly robust to change.

The economic case was therefore considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published a Technology Appraisal (number 82) in August 2004: tacrolimus and pimecrolimus for atopic eczema. This states that topical tacrolimus and pimecrolimus are not recommended for the treatment of mild atopic eczema or as first line treatments for atopic eczema of any severity. Topical calcineurin inhibitors are recommended, within their licensed indications, as second-line treatments after topical corticosteroids in moderate to severe disease.

Additional information: comparators

Tacrolimus ointment is licensed for second-line treatment in patients with moderate to severe atopic dermatitis not responding to conventional therapies. It is licensed for maintenance therapy in those with ≥ four disease exacerbations per year and who respond to initial twice daily treatment. There are no maintenance topical comparators for patients who are currently applying tacrolimus reactively.

Cost of relevant comparators

Drug	Dose regimen	Cost per 100gram (£)
Tacrolimus 0.1% ointment	**Applied twice weekly**	**66 to 72**

Costs from MIMs March 2010.

Additional information: budget impact

The manufacturer estimated the net drug budget impact for patients with moderate disease to be £48k in year 1 rising to £276k in year 5 based on 3,105 patients in year 1 and 3,556 patients in year 5. For patients with severe disease the manufacturer estimated there would be net drug budget savings of £8k in year 1 rising to £48k in year 5 based on 444 patients in year 1 and 508 patients in year 5. It was assumed that maintenance use of tacrolimus would replace 20% of the tacrolimus reactive treatment use in year 1 rising to 100% in year 5. Expert comments suggest that the market share assumptions may be overestimates.

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 12 February 2010.

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

The undernoted reference was supplied with the submission. The references shaded grey are additional to that supplied with the submission.

Wollenberg A, Reitamo S, Girolomoni G et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy 2008;63:742-50

European Medicines Agency (EMEA) European Public Assessment Report (EPAR) for tacrolimus (Proptic®), EMEA/H/000374/II/0034 www.emea.europa.eu

Hui RL, Lide W, Chan J et al. Association between exposure to topical tacrolimus or pimecrolimus and cancer. Ann Pharmacother 2009;43:1956-63