CICLOSPORIN 0.2% EYE OINTMENT (3.5g) (OPTIMMUNE®) FACT SHEET
TREATMENT OF OCULAR INFLAMMATORY CONDITIONS

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Ciclosporin 0.2% eye ointment (3.5g) (Optimmune®) can only be initiated in secondary care by an ophthalmologist specialising in corneal/external eye diseases.

Check List and Actions for GPs

- Practices must ensure that information sheet has been received from ophthalmologist with indication, likely duration of treatment and evidence that the specialist has discussed with the patient that the product is unlicensed.
- Practices must ensure that patient meets criteria for continuation of treatment (prescription initiated by an ophthalmologist specialising in corneal/external eye diseases and patient stabilised on treatment).
- Practices must ensure that repeat prescriptions will guarantee continuation of treatment until review.

Approved indications
Ciclosporin 0.2% eye ointment is recommended as a treatment option after first-line agents (e.g. ocular lubricants/steroids) have failed or are not tolerated for:

- Atopic Keratoconjunctivitis (AKC) & Vernal Keratoconjunctivitis (VKC)
- Dry Eye Disease (DED)/ Keratoconjunctivitis Sicca (KCS)
- Ocular Rosacea
- Thygeson’s keratitis & Chronic graft versus host disease

Available products
- Ciclosporin 0.2% eye ointment (3.5g tube); unlicensed veterinary medicine
- Drug Tariff price set (£79.57 / 3.5g Feb 2015)

Administration
- Dosage: Administer between once to four times daily
- Duration of therapy: Subject to the patient diagnosis. To be communicated in GP letter

Special Warnings and Precautions
- Therapeutic drug monitoring is not required for topically administered ophthalmic ciclosporin products.
Initiation
- To be initiated in secondary care only by an ophthalmologist specialising in corneal / external eye disease

Continuing / Reviewing / Discontinuing Ciclosporin 0.2% ointment (Optimmune®)
- Once patient has been stabilised on treatment (as deemed by corneal/external eye disease specialist) repeat prescribing and supply may be undertaken in primary care
- Ophthalmologist should provide information to GP including indication, likely duration of treatment and evidence that they have discussed with the patient that the product is unlicensed
- Evidence should also be provided that first-line treatments have failed
- Review / Discontinuation of therapy should be carried out by the corneal / external eye diseases specialist in secondary care
- Ophthalmic review is likely to be every three, six or twelve months

Storage
- Ciclosporin 0.2% eye ointment should not be stored below 25°C. Do not freeze
- Shelf life from manufacture: 104 weeks
- In use expiry: 28 days after opening

Adverse drug reactions (ADRs) reported
- Side effects from therapy are likely to be localised and not severe. Mild irritation is likely to occur in the first few days of therapy; blurred vision has also been reported

Associated risk
- No relevant risk has been associated to the use of ciclosporin 0.2% eye ointment
- Contact lens wear should be avoided unless under specialist advice

Further Information
- Therapeutic drug monitoring is not required for topically administered ophthalmic ciclosporin products

Procurement
- Ciclosporin 0.2% eye ointment can be obtained by Community Pharmacies from veterinary wholesalers or Moorfields Pharmaceuticals.
- The annual cost of treatment is between £ 954.84 and 1,909.68 depending on frequency per patient (cost taken from Drug Tariff £79.57 for 3.5g tube - accessed February 2015)

Appendices
- Appendix 1 – Quick Reference Guide
- Appendix 2 – Background and clinical information
- Appendix 3 – References
Appendix One: Quick Reference Guide

### Ciclosporin 0.2% preservative-free eye ointment (Optimmune)
Quick reference guide

<table>
<thead>
<tr>
<th><strong>Product name &amp; form:</strong></th>
<th>Ciclosporin A 0.2% preservative free eye ointment (Optimmune)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation:</strong></td>
<td>3.5g tube</td>
</tr>
<tr>
<td><strong>Category:</strong></td>
<td>Unlicensed medicine</td>
</tr>
</tbody>
</table>
| **Indications of Use:**  | 1. Management of severe allergic eye disease  
                          | 2. Severe dry eyes syndrome  
                          | 3. Prevention of corneal graft rejection  
                          | 4. Autoimmune keratoconjunctivitis e.g. vernal, atopic, staphylococcal hypersensitivity  
                          | 5. Thygeson’s keratitis  
                          | 6. Ligneous conjunctivitis  
                          | 7. Non-healing corneal erosions |
| **Rationale for Use:**   | No licensed alternative available                             |
| **Dose:**                | Apply 1 to 4 times each day                                   |
| **Duration of Treatment:**| Long-term (specific duration dependant on patient diagnosis) |
| **Cautions:**            | • Wash hands after use                                       |
|                          | • Do not use in pregnancy                                   |
|                          | • Do not use when there is fungal disease of the eye         |
| **Side effects:**        | Mild irritation in the first few days of treatment may occur  |
| **Monitoring:**          | No specific monitoring required as systemic absorption is minimal |
| **Storage:**             | Store below 25°C. Discard one month after opening            |
| **Other Information:**   | • Licensed as an animal medicine but has been manufactured to exactly the same standards as required for licensed human medicines  
                          | • Useful when patients cannot tolerate eye drops  
                          | • Contains paraffin base, maize oil and lanolin alchocol |
| **Ordering Information** | Moorfields Eye Hospital Pharmacy Department orders this product (Optimmune) directly from Moorfields Pharmaceuticals |
Appendix Two: Background and Clinical Information

Background
Ciclosporin A is a fungal antimitabolite used as an anti-inflammatory drug due to its ability to inhibit interleukin 2 activation of lymphocytes.\(^1\) It is used systemically to prevent graft rejection in organ and tissue transplantation as well as in the treatment of eczema and psoriasis.\(^2\) From the 1980s reports have highlighted that topical ciclosporin can be used to treat a variety of ocular inflammatory conditions including dry eye disease, vernal & atopic keratoconjunctivitis and ocular rosacea.\(^3,4,5\) Topical ciclosporin (CsA) also has niche applications in post adenovirus keratitis, Thygeson's keratitis and peripheral corneal melts (particularly Mooren's ulcer). Conventional long term treatment with topical steroids to reduce ocular inflammation risks severe adverse effects including cataract formation and increased intraocular pressure.\(^2\)

At present there are no topical ophthalmic ciclosporin preparations with a UK marketing authorisation for use in humans. However, various unlicensed preparations have been available from importers, veterinary manufacturers or specials manufacturers.

Many patients encounter difficulty upon trying to obtain topical ophthalmic ciclosporin in primary care due to a reluctance of GP’s to prescribe. Such decisions may be based on a lack of information regarding choice of product, indication for use, safety, treatment duration, licensing status, cost, availability and place in therapy. This protocol aims to provide information to accompany informed prescribing.

Choice of Product

Currently the only product available, accepted for use in North Central London is ciclosporin 0.2% eye ointment. Ciclosporin 2% eye drops and ciclosporin 0.06% eye drops are no longer manufactured. Ciclosporin 0.05% is not accepted for use at Moorfields Eye Hospital or in North Central London.

Dose

The dose for ciclosporin 0.2% eye ointment varies between applications once to four times daily, depending on clinical need. The dose must be clearly communicated to the patients GP.

Duration

Duration of therapy varies depending on clinical need. Long term therapy is often required. Patients who require long term therapy with topical ophthalmic ciclosporin will be reviewed by an ophthalmologist at regular intervals. Likely duration of therapy to be communicated to patient's GP by letter.

Initiation

Topical ophthalmic ciclosporin will be started in patients with the indicated diseases who have been found to be dependent on topical steroid to keep them free from sight-threatening ocular surface inflammation and/or free from severe and debilitating symptoms. No special tests or results are required before starting treatment.
Indications & Summary of Efficacy Data

1. **Dry Eye Disease (DED) / Keratoconjunctivitis sicca (KCS)**
   DED is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolality of the tear film and inflammation of the ocular surface. Use of lubricating eye drops does not directly address the ocular surface inflammation. Anti-inflammatory therapies should be considered for patients with moderate to severe disease with symptoms or evidence of corneal disease refractory to treatment. The role of ciclosporin in the treatment of dry eye was reviewed in the Report of the Management and Therapy Subcommittee of the International Dry Eye Work Shop (2007). This was a consensus document by a group of highly-respected experts on ocular surface disease, including one from the UK. The report concluded that anti-inflammatory therapies should be considered for patients with moderate to severe disease with symptoms or evidence of corneal disease refractory to treatment. As part of the literature search performed by Moorfields Eye Hospital, 12 trials were identified of which ten showed a demonstrable effect on dry eye. Further details of these trials can be obtained on request from the Moorfields Eye Hospital Medicines Management Team.

2. **Atopic Keratoconjunctivitis (AKC) & Vernal Keratoconjunctivitis (VKC)**
   AKC is a bilateral inflammatory ocular disease associated with atopic dermatitis. AKC is chronic in nature with frequent corneal complications which can cause permanent loss of vision. Aetiology involves a complex immunomodulatory dysfunction including type I and IV hypersensitivity reactions with Th1 cytokine profile. Corneal complications are seen in up to 70% of patients and approximately 30% require corneal transplantation.

   VKC is a seasonal chronic ocular allergic disease which is usually self-limiting. However in 5 -30% of cases permanent ocular changes may occur with associated visual impairment. The immunopathogenetic mechanism is complex and involves an IgE-mediated immediate hypersensitivity response as well as a Th2 type immune reaction.

   In both VKC and AKC it is not uncommon for patients to be dependent on topical steroid treatment to control their ocular surface inflammation. These patients are at significant risk of steroid-related ocular side-effects and this risk may be mitigated by use of topical ciclosporin to reduce or eliminate steroid-dependence.

   González-López et al (2012) conducted a Cochrane review on topical ciclosporin for atopic keratoconjunctivitis. The authors identified three RCTs with a total of 58 participants that were eligible for inclusion. One study reported on the use of 2% CsA in maize oil and two on the use of a commercial emulsion of 0.05% CsA. Of these three studies, one showed a beneficial effect of topical CsA in controlling signs and symptoms of AKC, one in controlling signs of AKC and one did not show evidence of an improvement. Only two studies analysed the effect of topical CsA in reducing topical steroid use; one showed a significant reduction in topical steroid use with CsA, but the other did not show evidence of this improvement. No serious adverse events were reported in the trials. The authors concluded that topical CsA may provide clinical and symptomatic relief in AKC and may help to reduce topical steroid use in patients with steroid-dependent or steroid-resistant AKC. The authors also remarked that no serious adverse events were identified in the trials.
A recent systematic review and meta-analysis of topical ciclosporin in allergic conjunctivitis reviewed results from 3 trials in AKC and 4 trials in VKC and concluded that the topical ciclosporin was more effective than placebo in alleviating the overall signs and symptoms of allergic conjunctivitis. However, the clinical and methodological heterogeneities in the studies mean that the overall efficacy should be interpreted with caution.\textsuperscript{16}

A literature search conducted at Moorfields Eye Hospital found 14 trials where topical ciclosporin was used for atopic or vernal keratoconjunctivitis, of which 13 showed a demonstrable effect. Further details of these trials can be obtained on request from the Moorfields Eye Hospital Medicines Management Team.

3. Ocular Rosacea

Rosacea is an oculo-cutaneous inflammatory disorder which affects the facial sebaceous glands and the meibomian glands of the eyelid. Ocular rosacea is characterised by blepharo-keratoconjunctivitis, which can range from mild punctate epithelial erosions to significant corneal neovascularization and thinning. The skin shows erythema, telangiectasia and pustules over the cheeks, nose, and forehead with thickening over the nose (rhinophyma) in the later stages of this potentially sight threatening condition. The precise pathophysiology is unknown although a proposed theory is delayed type hypersensitivity like reaction. The traditional mainstay of treatment is similar to that of posterior blepharitis with topical antibiotics and steroids.\textsuperscript{7}

Van Zuuren et al (2011) conducted a Cochrane review on interventions for rosacea and concluded that ciclosporin 0.05% ophthalmic emulsion appears to be more effective than artificial tears for rosacea of the eyes.\textsuperscript{17} The authors identified ciclosporin as the only drug for which there was high grade evidence of effect in the disease, based on one RCT by Schechter et al (2009).\textsuperscript{18}

4. Niche applications in ocular surface inflammatory diseases

There are case series supporting the use of topical cyclosporine in a variety of chronic ocular surface inflammatory diseases such as Thygeson’s keratitis and chronic graft versus host disease.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Disease</th>
<th>Trial characteristics</th>
<th>Number of patients (experimental / control)</th>
<th>Side effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinhard T et al\textsuperscript{19}</td>
<td>1996</td>
<td>Thygeson’s keratitis</td>
<td>Case series 2% CsA 3 times Daily for a month with reducing regimen over 6 months</td>
<td>31 eyes of 17 patients</td>
<td>Burning and stinging</td>
<td>Complete resolution of opacities in 21/31 at 6 months. Partial resolution in a further 8/31.</td>
</tr>
<tr>
<td>Lelli GJ et al\textsuperscript{20}</td>
<td>2006</td>
<td>Graft versus host disease</td>
<td>Case series 0.05% - 2% CsA 2-4 times Daily</td>
<td>32 eyes of 16 patients</td>
<td>Irritation, burning</td>
<td>Corneal fluorescein staining improved in all patients. Dry eye symptoms improved in 10 patients (62.5)</td>
</tr>
</tbody>
</table>
Safety & monitoring
No significant systemic adverse effects have been reported in any of the trials found. Restasis has been used in the US since 2003. The most common adverse reaction reported on the Restasis prescribing information sheet is ocular burning (17%). Other reactions reported in 1% to 5% of patients included conjunctival hyperaemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).\(^{21}\)

Barber et al (2005) conducted a phase III, follow on, non-randomized safety evaluation of ciclosporin 0.1% ophthalmic emulsion, administered twice daily to dry eye disease patients. 412 adult patients, previously treated with ophthalmic ciclosporin, were treated for up to 3 years (mean duration of 19.8 months). The authors concluded ciclosporin was safe, well tolerated, and not associated with systemic side effects.\(^{22}\) The most common treatment-related adverse events were localised burning sensation (10.9%), stinging (3.9%) and conjunctival hyperaemia (3.4%).

The only other option open to patients with chronic inflammatory conditions are topical steroids which have a poor adverse effect profile, particularly in long term treatment. These adverse effects include cataract and raised intraocular pressure. When treated with topical steroids for 4–6 weeks 5% of the population demonstrated a rise in intraocular pressure greater than 16 mmHg and 30% demonstrated a rise of 6–15 mmHg.\(^{23,24}\) Patients using topical steroids require regular monitoring at 2-6 monthly follow up visits to screen for adverse effects whereas stable patients on CSA may be reviewed once per year.

Therapeutic drug monitoring is not required for topically administered ophthalmic ciclosporin products.

Supply
Initial supply will be made by the hospital pharmacy. Once stable, as judged by external / corneal ophthalmologist, the patient may obtain further supplies from primary care, subject to providing the GP with relevant information containing indication, likely duration of treatment and evidence that a discussion with the patient has taken place regarding the unlicensed nature of the product.

Ciclosporin 0.2% eye ointment is listed in the Drug Tariff and should be reimbursed only in accordance with the most current Drug Tariff price. Community pharmacies can order ciclosporin 0.2% eye ointment from any veterinary wholesaler e.g. Centaur or Moorfields Pharmaceuticals. Delivery can usually be made to community pharmacy by the next working day.
Appendix Three: References
