Ciclosporin A (Cyclokat) for keratoconjunctivitis sicca

**Target group**
- Keratoconjunctivitis sicca: severe – first line; in combination with ocular lubricants.

**Technology description**
Ciclosporin A (Cyclokat; Nova22007) is a cationic emulsion of ciclosporin A, based on Novagali’s Novasorb® technology. The positively-charged emulsion electrostatically adheres to the negatively-charged epithelial layer of the eye, thereby improving ocular absorption. Ciclosporin A is an immunomodulating drug that acts to reduce ocular inflammation associated with dry eye syndrome by enhancement or restoration of lacrymal gland secretion. Cyclokat is intended for the treatment of severe keratoconjunctivitis sicca. It is administered topically at a concentration of 1mg/ml (0.1% w/w) once daily.

Cyclokat is also in phase III clinical trials for vernal keratoconjunctivitis (allergic conjunctivitis affecting children).

**Innovation and/or advantages**
If licensed, cyclokat would offer an additional treatment option associated with reduced irritation compared with existing (unlicensed) ciclosporin A preparations.

**Developer**
Novagali (now part of Santen group).

**Availability, launch or marketing dates, and licensing plans**
In phase III clinical trials.

**NHS or Government priority area**
This topic is relevant to The National Service Framework for long-term conditions (2005) and The National Service Framework for older people (2001).

**Relevant guidance**
- NHS Clinical Knowledge Summary. Dry eye syndrome. 2008¹.

**Clinical need and burden of disease**
Keratoconjunctivitis sicca, also known as dry eye syndrome, is a common condition caused by a disorder of the tear film. Tear deficiency or excessive tear evaporation causes irritation of the external surface of the eye, resulting in discomfort, pain and blurred vision¹,². Although estimates of prevalence vary, the condition is more common in older people, with reported prevalence rates of 15-33% in people aged 65 and over¹. It is also around 50% more common in women than in men¹, and can have significant effects on quality of life and common vision-related daily activities, such as driving and reading³. Keratoconjunctivitis sicca is not usually a serious condition, however severe cases can result in scarring, corneal ulcers and visual impairment²,⁴. It is also associated with several other conditions such as graft vs host disease, and several rheumatological disorders such as Sjögren’s syndrome, systemic lupus erythematosus and rheumatoid arthritis⁵. In 2011, in England and Wales there were over 6.6 million prescription items for artificial tears, ocular lubricants and astringents dispensed in the community at a cost of over £34.2 million⁵,⁶.
**Existing comparators and treatments**

There is no cure for keratoconjunctivitis sicca, however a range of treatments are available to control symptoms. Current treatment options for severe disease include:

- Preservative-free artificial tears – hypromellose, carbomers, carmellose sodium, hydroxyethylcellulose, sodium hyaluronate.
- Lubricating eye ointments – liquid paraffin.
- Specialised eyeware – moisture chamber spectacles, contact lenses.
- Tetracyclines.
- Secretagogues.
- Anti-inflammatory agents – topical ciclosporin A (currently unlicensed; limited use due to irritation and blurred vision), corticosteroids (non-preserved dexamethasone, prednisolone), topical tacrolimus (not licensed for ocular use), omega-3 fatty acids.
- Autologous serum tears.
- Surgery – punctual occlusion or salivary gland autotransplantation.

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants and schedule</th>
<th>Follow-up</th>
<th>Primary outcomes</th>
<th>Secondary outcomes</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siccanove, NCT00814515; ciclosporin A 0.1% vs placebo; phase III.</td>
<td>Novagali Pharma.</td>
<td>Complete and published in abstract.</td>
<td>Trial registry, abstract, manufacturer.</td>
<td>EU.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=492; adults; dry eye syndrome; moderate to severe. Randomised to ciclosporin A (0.1%) ophthalmic emulsion once daily vs vehicle with no active pharmacological component, once daily.</td>
<td>Active treatment period 6 months.</td>
<td>Corneal fluorescein staining (CFS); ocular discomfort.</td>
<td>Ocular symptom disease index questionnaire; % of complete responders (measured using CFS).</td>
<td>Cyclokat vs vehicle: mean CFS at month 1, -0.77 vs -0.52 (p=0.002), month 3, -0.92 vs -0.70 (p=0.03), and month 6, -1.05 vs -0.82 (p=0.009). Post hoc analysis revealed better outcomes in cyclokat-treated patients with higher CFS scores at baseline. Complete corneal clearing at month 3 and 6 was superior with Cyclokat only in patients with CFS grade 2 at baseline.</td>
</tr>
<tr>
<td>Sansika, EUCTR2011-000160-97-GB; cyclokat vs placebo; phase III.</td>
<td>Novagali Pharma.</td>
<td>Ongoing.</td>
<td>Trial registry.</td>
<td>EU and USA.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=252 (planned); adults; persistant dry eye syndrome; severe. Randomised to ciclosporin A 1mg/ml ophthalmic emulsion once daily vs vehicle with no active pharmacological component, once daily.</td>
<td>Active treatment period 6 months with a follow-up period of 6 months.</td>
<td>CFS; ocular tolerability; ocular safety.</td>
<td>Shirmer test; complete corneal clearing; artificial tear use; efficacy.</td>
<td>-</td>
</tr>
</tbody>
</table>

- Adverse effects (AEs)
- Most frequently reported AEs included eye irritation (15.2%), eye pain (9.5%), instillation site irritation (9.5%).

\* Expert opinion.
meibomianitis (8.6%) and lacrimal disorder (7.4%). A higher incidence of ocular AEs were shown with Cyclokat vs vehicle.

| Expected reporting date | - | Expected study completion date Q3/4 2012. |

**Trial**
NCT00739349; ciclosporin vs placebo; phase II.

**Sponsor**
Novagali Pharma.

**Status**
Complete but unpublished.

**Source of information**
Trial registry, manufacturer.

**Location**
USA.

**Design**
Randomised, placebo-controlled.

**Participants and schedule**
n=132; adults; dry eye in both eyes. Randomised to ciclosporin A ophthalmic cationic emulsions 0.05%, 0.1% or vehicle with no active pharmacological component, all once daily.

**Follow-up**
Active treatment period 3 months.

**Primary outcomes**
Safety; efficacy.

**Key results**
Cyclokat 0.1% was superior to vehicle for tear film break-up time (TFBUT), with a difference of 1.31 seconds. TFBUT improvement was associated with improvement of several symptoms of dry eye, including foreign body sensation, itching and eye dryness.

**Estimated cost and cost impact**
The cost of Cyclokat is not yet known. The cost of selected comparator treatments are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost</th>
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</thead>
<tbody>
<tr>
<td>Hypromellose 0.3%</td>
<td>As required</td>
<td>£1.39 for 10ml.</td>
</tr>
<tr>
<td>Carbomers (Clinitas Gel) 0.2%</td>
<td>3-4 times daily or as required.</td>
<td>£1.49 for 10g</td>
</tr>
<tr>
<td>Sodium hyaluronate (Hyabak) 0.15%</td>
<td>As required</td>
<td>£7.99 for 10ml.</td>
</tr>
<tr>
<td>Carmellose sodium (Optive) 0.5%</td>
<td>As required</td>
<td>£7.49 for 10ml.</td>
</tr>
<tr>
<td>Liquid paraffin (Lacri Lube).</td>
<td>Application before sleep.</td>
<td>£2.51 for 3.5g.</td>
</tr>
<tr>
<td>Dexamethasone (Maxidex) 0.1%</td>
<td>4-6 times daily.</td>
<td>£2.80 for 10ml.</td>
</tr>
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</table>

**Claimed or potential impact – speculative**

**Patients**
- Reduced mortality or increased length of survival
- Other:

- Reduction in associated morbidity or improved quality of life for patients and/or carers

- Quicker, earlier or more accurate diagnosis or identification of disease

- None identified

**Services**
- Increased use
- Decreased use

- Service organisation
- Staff requirements

- Other:

- None identified

**Costs**
- Increased unit cost compared to alternative

- New costs: additional treatment option.

- Increased costs: more patients coming for treatment

- Increased costs: capital investment needed

- Savings:

- Other:
Other issues

☑ Clinical uncertainty or other research question identified: Expert opinion indicates research required to determine whether ciclosporin A 0.1% can replace the use of topical steroids. Expert opinion also suggests that the outcome measures should include more objective markers of disease activity e.g. tear film osmolarity, conjunctival keratinisation, dysplasia, expression on HLA-DR and changes in ocular surface features through immunohistochemical analysis for goblet cells.

References

12 ClinicalTrials.gov. NOVA22007 0.05% and 0.1% cyclosporine versus vehicle for the treatment of dry eye. http://www.clinicaltrials.gov/ct2/show/NCT00739349?term=NOVA22007&rank=1 Accessed 5 April 2012.

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b Expert opinion.