

ciclosporin 1mg/mL (0.1%) eye drops emulsion (Ikervis[®])

SMC No. (1089/15)

Santen GmbH

4 September 2015

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ciclosporin 1mg/mL (0.1%) eye drops emulsion (Ikervis[®]) is accepted for use within NHS Scotland.

Indication under review: treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Ciclosporin eye drops, compared to vehicle, improved signs of corneal surface damage but not symptoms in patients with severe keratitis associated with dry eye disease.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Dosing Information

One drop once daily to be applied to affected eye(s) at bedtime. Patients should be instructed to use nasolacrimal occlusion and to close the eyelids for 2 minutes after instillation, to reduce the systemic absorption. This may result in a decrease in systemic undesirable effects and an increase in local activity. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 15 minutes apart. Ciclosporin eye drops should be administered last.

Response to treatment should be reassessed at least every six months. Treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology.

Product availability date

July 2015.

Summary of evidence on comparative efficacy

Ciclosporin is an immunosuppressant that has anti-inflammatory effects. It inhibits production and/or release of pro-inflammatory cytokines, including interleukin 2 (IL-2) or T-cell growth factor and increases release of anti-inflammatory cytokines. These may contribute to effects in dry eye disease, which is thought to be mediated by inflammatory and immunological mechanisms.¹ Ciclosporin eye drops is the first ophthalmic formulation of ciclosporin licensed in the UK and it is indicated to treat severe keratitis (inflammation of the cornea) in patients with dry eye disease, which has not improved with tear substitutes.

The pivotal phase III double-masked study (SANSIKA) recruited 245 adults with persistent severe dry eye disease defined by corneal fluorescence staining (CFS) score of 4 on the modified Oxford scale; Schirmer test without anaesthesia score of less than 10mm per 5 minutes (but not lower than 2mm per 5 minutes); and Ocular Surface Disease Index (OSDI) score of at least 23. They were randomised with stratification for centre in a 2:1 ratio to ciclosporin 0.1% eye drops or vehicle eye drops, one drop in each eye once daily at bedtime for six months. The primary outcome was assessed in the worst eligible eye and was the proportion of patients who had both a CFS response, defined as an improvement of at least 2 points from baseline on the modified Oxford scale, and an OSDI response, defined as improvement of at least 30% from baseline in OSDI. This was evaluated in the full analysis set, which comprised all randomised patients who received study drug, using imputed data in a logistic regression model with treatment and pooled country as factors.²

There was no significant difference between ciclosporin eye drops and vehicle eye drops for the primary outcome, proportion of patients achieving both CFS and OSDI responses, 29% (44/154) versus 23% (21/91), respectively. Non-significant effects were observed in sensitivity analyses. There were no significant differences between ciclosporin eye drops and vehicle eye drops for secondary outcomes of proportions of patients achieving complete corneal clearing, 6.5% (10/154) versus 4.4% (4/91); responses on modified Oxford scale (defined as improvement of at least 2 points), 52% (80/154) versus 45% (41/91); OSDI (defined as improvement of at least 30%), 40% (61/154) versus 40% (36/91); and global visual analogue scale (VAS) assessment of ocular discomfort (defined as

improvement of at least 30%), 31% (48/154) versus 37% (34/91), respectively; or in mean change from baseline to month six for National Eye Institute vision function questionnaire (NEI-VFQ-25); EQ-5D summary index or EQ-5D VAS score.²

There was a significant improvement with ciclosporin eye drops compared with vehicle eye drops in CFS assessed on modified Oxford scale over time, with adjusted mean change from baseline at three months of -1.51 versus -1.13, ($p=0.024$), and at six months of -1.76 versus -1.42, ($p=0.037$), respectively. With ciclosporin eye drops, compared with vehicle eye drops, there was a significant reduction in human leukocyte antigen-DR (HLA-DR) expression on conjunctival cell surface at months one and six. There was no significant difference between the groups for change in percentage of HLA-DR+ cells at months one and six.²

In post-hoc analyses, where CFS response was defined as an improvement of at least 3 points on the modified Oxford scale, the proportion of patients achieving CFS plus OSDI responses was significantly higher with ciclosporin eye drops compared with vehicle eye drops, 18% (29/154) versus 7.7% (7/91) respectively, $p=0.016$ (using analysis similar to the primary analysis); and 21% (28/131) versus 8.5% (7/82), $p=0.012$ (using observed data). Similar results were observed in post-hoc analyses of CFS responders using the 3 points criterion, 31% (48/154) versus 13% (12/91) respectively, $p=0.002$ (using analysis similar to the primary analysis); and 36% (47/132) versus 14% (12/83), $p=0.001$ (using observed data).²

A supportive double-masked phase III study (SICCANOVE) recruited 489 adults with persistent moderate to severe dry eye disease defined by at least one moderate to severe symptom of dry eye with a score of at least 2 (on a 4-point scale); CFS score of at least 2 but not greater than 4 on the modified Oxford scale; Schirmer test without anaesthesia score of less than 10mm per 5 minutes (but not lower than 2mm per 5 minutes); tear break-up time (TBUT) of 8 seconds or less; and lissamine green staining greater than 4. They were randomised with stratification for Sjogren's syndrome in a 1:1 ratio to ciclosporin 0.1% eye drop or vehicle eye drops one drop in each eye once daily at bedtime for six months. The co-primary outcomes were change from baseline to day 168 in (1) CFS measured on modified Oxford scale and (2) global score of ocular discomfort unrelated to study medication instillation measured on a VAS. These were evaluated in the worst eligible eye within the full analysis set, which comprised all randomised patients with post-treatment efficacy evaluations and those who withdrew due for reasons related to study medication prior to undergoing efficacy evaluations. Data were analysed by analysis of covariance (ANCOVA) which included treatment, Sjogren's status and baseline scores, with last observation carried forward for missing data.²

In the ciclosporin eye drop group, compared with the vehicle eye drop group, mean change from baseline to day 168 in CFS assessed on the modified Oxford scale was significantly greater: -1.05 and -0.82, respectively. There was no significant difference between the ciclosporin eye drop and vehicle eye drop groups for the other co-primary endpoint, mean change from baseline to day 168 in global ocular discomfort on the VAS scale; -12.82 and -11.21, respectively, indicating improvement in both groups.²

Post-hoc analyses were conducted using data from 85 (17%) patients in the SICCANOVE study who had severe dry eye disease, defined (as in the SANSIKA study) as modified Oxford scale grade 4 at baseline. In this subgroup, ciclosporin eye drops, compared with vehicle eye drops, was associated with a significantly greater decrease from baseline to day 168 in modified Oxford score; -1.47 versus -0.69, $p=0.002$; and a higher percentage of CFS plus OSDI co-responders (responses defined as in SANSIKA study primary analysis), 33% versus 7.1%, $p=0.003$.²

Meta-analyses of pooled data from the SANSIKA and SICCANOVE studies (using analysis and methodology as in SANSIKA study) indicated that the proportion of patients achieving CFS plus OSDI responses at six months was significantly greater with ciclosporin eye drops compared with vehicle

eye drops in the full analysis set (n=734), 22% versus 13% (p=0.015), and the subgroup with severe disease, defined as CFS grade 4 and OSDI at least 23 (n=319), 30% versus 18% (p=0.038).²

Summary of evidence on comparative safety

The main adverse events with ciclosporin eye drops appear to be related to ocular discomfort when administering the medicine. Pooled data from SANSIKA, SICCANOVE and two phase II studies indicate that the most common ocular adverse events considered by the investigator as possibly related to ciclosporin were: instillation site pain, 16%; instillation site irritation, 9%; eye irritation, 8.8%; eye pain, 3.5%; instillation site lacrimation, 2.9%; lacrimation increased, 2.1%; instillation site erythema, 1.9%; ocular hyperaemia, 1.9%; conjunctival hyperaemia, 1.7%; erythema of eyelid, 1.7%; eyelid oedema, 1.3% and blurred vision, 1.2%.²

Pooled data from the SANSIKA and SICCANOVE studies during the double-blind phase within the ciclosporin eye drops and vehicle eye drops groups indicate that rates of adverse events were 56% (221/396) and 47% (161/340), but rates of treatment-related adverse events were higher with ciclosporin, 36% (142/396) and 20% (69/340), respectively. In the respective groups within the 221 and 161 patients who had an adverse event, the maximum severity of adverse event was severe for 44% (98/221) and 33% (52/161) of patients; and within the 142 and 69 patients who had a treatment-related adverse event, the maximum severity of treatment-related adverse event was severe for 61% (86/142) and 51% (35/69) of patients. Treatment-related serious adverse events were reported by one patient in each group. In the ciclosporin eye drops and vehicle eye drops groups, study drug was discontinued by 12% (48/396) and 10% (35/340) due to adverse events; and by 9.3% (37/396) and 6.8% (23/340) due to treatment-related adverse events, respectively. Systemic adverse events were reported by similar proportions of patients in the ciclosporin eye drops and vehicle eye drops groups, 24% versus 28%, with 3.5% and 4.4%, respectively, considered treatment-related. The majority were mild to moderate and no serious systemic adverse events were reported.²

The summary of product characteristics notes that patients receiving immunosuppressive therapies, including ciclosporin, are at increased risk of infections. Generalised and localised infections can occur. Pre-existing infections may also be aggravated. Cases of infections have been reported uncommonly in association with the use of ciclosporin 1% eye drops (Ikervis®).¹

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Ciclosporin eye drops are the first ophthalmic formulation of ciclosporin licensed in the UK. For several years treatment of dry eye has included specially compounded ciclosporin eye drops and imported products licensed in other countries,² e.g. ciclosporin 0.05% ophthalmic emulsion (Restasis®), which is administered to the affected eye(s) as one drop twice daily.⁵

Within an ad-hoc expert meeting during the European Medicines Agency (EMA) review it was noted that treatment of dry eye disease should aim to control the underlying disease and in addition to this, available treatments include artificial tears or lubricants for symptoms, with anti-inflammatory preparations for more severe forms of disease, including short-term corticosteroids and topical ciclosporin (compounded or imported). Autologous serum was also considered beneficial. However, it was noted that the medicines currently used in practice do not have a demonstrated effect on clinical signs and many patients continue to suffer impaired function, pain and irritation. There was a consensus that there is an unmet medical need in this disease.²

Clinical experts consulted by SMC also considered that there is unmet need in this therapeutic area, namely anti-inflammatory medications that can be used long-term and are steroid sparing.

The pivotal study failed to achieve the primary outcome of demonstrating an effect relative to vehicle control for the proportion of patients having both a response in terms of improvement of corneal damage (CFS, modified Oxford scale) and symptoms of ocular discomfort (OSDI). However, the secondary outcome of mean change from baseline in modified Oxford scale was significantly improved, relative to vehicle control, with ciclosporin and this was also observed in the supportive study, although the supportive study also failed to demonstrate a significant effect on symptoms, the other co-primary outcome. During the EMA review, an ad-hoc expert panel noted that there is no clear correlation between signs of corneal damage and symptoms, especially in severe forms of dry eye disease, where multiple factors including a loss in ocular surface sensitivity may affect symptoms. They considered that an effect on signs alone, if large enough, could be clinically relevant; however, differing opinions were expressed about the clinical relevance of the effect of ciclosporin on signs of corneal damage. The Committee for Medicinal Products for Human Use (CHMP) concluded in relation to this that the difference between treatments was moderate, but, taking into account the experts' view, it was considered clinically meaningful. It was also noted that ciclosporin eye drops reduce ocular inflammation (as evidenced by the effect on HLA-DR) and this was considered of relevance as it may help disrupt the vicious disease cycle of dry eye disease.²

The significant improvement with ciclosporin compared with vehicle, in corneal surface damage on CFS, on the modified Oxford scale was 0.35units. When this is translated into number of dots of staining, i.e. corneal lesions, it represents a between group difference of on average 50% more dots/lesions with vehicle compared with ciclosporin, which was considered by the CHMP to be clinically meaningful.²

As the primary outcomes were not achieved in the pivotal study and for one co-primary outcome in the supportive study, evidence of efficacy has been derived from secondary outcomes, post-hoc and subgroup analyses. The evidence from these types of analyses may be less robust.

The SANSIKA and SICCANOVE studies both excluded patients with a score of 5 on the modified Oxford scale.² These patients would have the most extensive corneal surface damage. The effect of ciclosporin eye drops in this group of patients is unclear.

Other formulations of ciclosporin, from 0.05% to 2% ophthalmic emulsions in olive or castor oil, up to four times daily, have been used in clinical practice as an alternative to steroids in severe forms of dry eye disease for several decades.² Recent systematic reviews of ciclosporin in dry eye disease have been published; however, these were limited by heterogeneity in terms of in outcomes, scales and time-points of outcome evaluation and noted that differences in aetiology and severity of the disease may also confound the assessments.⁶⁻⁸

Clinical experts consulted by SMC considered that ciclosporin eye drops is a therapeutic advancement due to its long-term anti-inflammatory and steroid-sparing effects. It has advantages over the currently used unlicensed topical ciclosporin preparations, which are specially compounded or imported. They also considered that the place in therapy of ciclosporin eye drops is for the treatment of patients with dry eye disease that has not responded to tear substitutes. It would be used in place of specially compounded or imported formulations of ciclosporin eye drops, which are associated with issues related to tolerability, quality and supply.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing ciclosporin plus artificial tears to artificial tears alone for the treatment of severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes. A Markov model was used consisting of 6 health states (treatment induction, treatment responder, non-responder, temporary punctual plug, permanent punctual plugs and post punctual plugs). Patients moved through the model according to response to treatment. Patients categorised as responders had a higher quality of life than non-responders and required less artificial tear use. The time horizon was 30 years.

A post-hoc analysis based on the clinical data from the pivotal study, SANSIKA, was used to inform the economic analysis. It should be noted that the comparator in the SANSIKA study (vehicle) was used as a proxy for artificial tear use in clinical practice. The primary outcome in the SANSIKA study was the proportion of patients achieving both a CFS response (improvement of at least 2 points from baseline on the modified Oxford scale), and an OSDI response (improvement of at least 30% from baseline in OSDI) but in the economic analysis the company used a post-hoc definition of response (improvement of at least 3 points from baseline on the modified Oxford scale) and an OSDI response (improvement of at least 30% from baseline in OSDI). Based on this post-hoc definition of response, the response rates at 6 months were estimated to be 18.8% and 7.7% for ciclosporin plus artificial tears and artificial tears alone respectively.

Utility values were derived from the SANSIKA study using the EQ-5D questionnaire (administered at baseline and 6 months). A baseline utility of 0.66 was estimated while responders were associated with a utility gain of 0.0736 and non-responders were associated with a utility decrement of -0.0040. In order to validate these values, the company compared the estimates to a published study, in which the values were somewhat similar. However, due to inherent differences between the published study and SANSIKA study, there is some uncertainty surrounding the utility gain.

Drug acquisition costs were included in the analysis. As the treatment is self administered, no administration costs were included. Resource use (rate of ophthalmologist visits, tests, monitoring etc) for both treatment arms is the same and did not differ according to response to treatment, other than the inclusion of the costs of artificial tears for non-responders.

Compared to artificial tears alone ciclosporin resulted in a base case incremental cost-effectiveness ratio (ICER) of £19,080 per quality-adjusted life-year (QALY). This is based on an incremental QALY gain of 0.037 and an incremental cost of £711.

The company included a range of sensitivity analysis including one-way, scenario and probabilistic sensitivity analysis (PSA). The one-way sensitivity analysis indicated that results were most sensitive to a change in the utility value for a responder. When this value was decreased to 0.67 (from 0.72) the ICER increased to £164,997. In the scenario analysis where the definition of response from the SANSISKA study is used i.e. CFS \geq 2 and OSDI \geq 30%, the ICER increased to £33,215 per QALY. The results of the PSA showed there was a 70% probability that ciclosporin was cost-effective at a willingness to pay threshold of £30k per QALY.

There were a number of weaknesses with the analysis:

- Based on SMC expert responses, artificial tears alone may not be the most appropriate comparator. Potential alternative treatments mentioned by the clinical experts include continuous therapy with ciclosporin eye drops, a short course of topical corticosteroid eye drops or a short course of topical corticosteroid eye drops followed by continuous therapy with ciclosporin eye drops. The company justified the selection of artificial tears alone, and

identified a number of concerns surrounding a possible comparison with topical corticosteroid eye drops, by citing a lack of published clinical evidence in patients with severe dry eye disease as a major difficulty in performing a robust comparison. While some uncertainty remains surrounding the appropriateness of the comparator, it was acknowledged that unlicensed formulations of ciclosporin are currently used in practice and a scenario analysis provided by the company showed the weighted average cost of these unlicensed formulations is marginally higher than the cost of ciclosporin eye drops.

- There is some concern surrounding the face validity of the utility values derived from the pivotal study, SANSIKA, i.e. the baseline value for responders (0.66) may be too low. The company tried to validate the utility values via a comparison to a published study, however due to inherent uncertainties within this study, there remains some doubt the appropriateness of these values. The company subsequently provided some additional analysis in which the utility gain for responders (0.0736) is reduced. This analysis showed that when the utility gain was reduced by 30% to 0.054, the ICER increased to £27k.
- A post-hoc definition of response was used to derive responder rates in the economic analysis (CFS of at least 3 and OSDI of at least 30%). The company justified the use of the post-hoc definition, stating that it provides a greater predictor of change from baseline utility at 6 months and a significant p value. It is worth noting that the company also provided scenario analysis using the original definition as noted in the SANSIKA study. Based on this analysis, the ICER increased to £33k.
- As the transition probabilities are maintained over the duration of the 30 year time horizon, ciclosporin is assumed to be more effective than artificial tears alone. To test this assumption of continued benefit, the company was asked to provide an analysis using more conservative transition probabilities. When the same probability of transitioning from response to non-response was applied to both treatment arms the ICER increased to £20k. This analysis still assumed a higher proportion of patients respond to ciclosporin and artificial tears than with artificial tears alone based on the post-hoc analysis response rates.
- In order to test the combined uncertainty in the model, the company provided a scenario analysis which applied the same transition probabilities in both treatment arms and a reduced utility gain for responders by 30%. In this analysis, the ICER increased to £29k.

Despite the weaknesses outlined above, the economic case has demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

There are no published guidelines from the Scottish Intercollegiate Guidelines Network (SIGN), National Institute for Health and Care Excellence (NICE) or Royal College of Ophthalmologists for the treatment of dry eye disease.

In 2013 the American Academy of Ophthalmology published preferred practice pattern (PPP) for dry eye syndrome. This noted that anti-inflammatory therapies may be considered in addition to aqueous enhancement therapies for moderately severe dry eye. These include ciclosporin eye drops. Results

from some clinical studies and limitations of the evidence were detailed and it was noted that the lack of long-term data on effectiveness of ciclosporin and costs of longer-term treatment should be weighed against the expected benefits. It was also noted that there was uncertainty around whether the effects observed in the clinical studies were clinically significant, and that many subgroups of dry eye patients (e.g. those with meibomian gland disease or keratoconjunctivitis sicca) are unlikely to experience the same benefits.⁹

In 2007 the International Dry Eye Work Shop (DEWS) published its report. Within the section on management and therapy, topical anti-inflammatory preparations, ciclosporin or corticosteroids, were recommended for patients with dry eye disease severity level 2 assessed on the modified International Task Force (ITF) delphi panel severity scale, which ranges from 1 to 4. Level 2 is associated with moderate episodic or chronic ocular discomfort.¹⁰

Additional information: comparators

None. Ciclosporin eye drops are likely to be used in addition to tear substitutes and ocular lubricants. Unlicensed preparations of ciclosporin eye drops are currently in clinical use.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Ciclosporin eye drop	One drop to affected eye(s) once daily	874

Costs from new product assessment form.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 7071 in each year with an estimated uptake rate of 10% in year 1 (707 patients) and 66% (3,967 patients) in year 5. A discontinuation rate of 15% was applied in year 5.

The gross impact on the medicines budget was estimated to be £611k in year 1 and £3.4m in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £503k in year 1 and £2.8m in year 5.

These company estimates assume displacement of artificial tears only and therefore if unlicensed formulations of ciclosporin are displaced in practice the net budget impact will be lower. In addition, SMC clinical experts and ISD prescribing data from 2013/14 indicate the patient population estimated by the submitting company may be significantly overestimated.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Santen. Summary of product characteristics for Ikervis[®], last updated on 19.3.15.
2. European Medicines Agency. European public assessment report for Ikervis, CHMP assessment report, EMA/CHMP/473489/2014, 22 January 2015.
3. Santen. Clinical study report for NVG10E117 (SANSIKA), 31 October 2013.
4. Santen. Clinical study report for NVG06C103 (SICCANOVE), 10 August 2010.
5. US Food and Drug Administration. Label for Restasis[®], last revised November 2012.
6. Sacchetti M, Mantelli F, Lambiase A et al. Systematic review of randomised clinical trials on topical ciclosporin A for the treatment of dry eye disease. Br J Ophthalmol 2014; 98: 1016-22.
7. Zhou XQ and Wei RL. Topical ciclosporin A in the treatment of dry eye: a systematic review and meta-analysis. Cornea 2014; 33: 760-67.
8. Aragona P. Topical cyclosporine: are all indications justified?. Br J Ophthalmol 2014; 98: 1001-2.
9. American Academy of Ophthalmology. Preferred practice pattern (PPP) for dry eye syndrome, 2013.
10. Pflugfelder SC, Geerling G, Kinoshita S, et al. Management and Therapy of Dry Eye Disease: Report of the Management and Therapy Subcommittee of the International Dry Eye Work Shop (2007). Ocular Surface 2007; 5 (2): 163-178.

This assessment is based on data submitted by the applicant company up to and including 14 August, 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.

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.