

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

### **Ciclosporin for treating dry eye disease which has not improved after treatment with artificial tears**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ciclosporin in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ciclosporin in the NHS in England.

For further details, see the Guides to the technology appraisal process.

**The key dates for this appraisal are:**

Closing date for comments: 15 July 2015

Second Appraisal Committee meeting: 18 August 2015

Details of membership of the Appraisal Committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

## 1 Appraisal Committee's preliminary recommendations

1.1 The Committee is minded not to recommend ciclosporin within its marketing authorisation, that is, for treating severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

1.2 The Committee recommends that NICE requests further analyses from the company, which should be made available for the second Appraisal Committee meeting, and should include:

- An indirect comparison of the clinical effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, and that of corticosteroids (if needed) and artificial tears.
- An economic model comparing the cost effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, with that of corticosteroids (if needed) and artificial tears. This cost effectiveness analysis should include:
  - the original SANSIKA Corneal Fluorescein Staining – Ocular Surface Disease Index (CFS-OSDI) definition of response (that is, improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI)
  - an evidence-based treatment stopping rates with ciclosporin plus corticosteroids (if needed) and artificial tears
  - changes to resource use and costs reflecting:
    - ◇ that artificial tears may be used alongside punctal plugs

- ◇ both a baseline average and a 6-month average for the number of artificial tear drops used per day, for both treatment groups
- ◇ the assumption that ciclosporin is dispensed and costs are incurred monthly
- sensitivity analyses using different utility values for response by treatment group
- a subgroup analysis for people with Sjögren’s syndrome and severe dry eye disease.

## **2 The technology**

- 2.1 Ciclosporin (Ikervis, Santen Pharmaceutical) is a sterile, positively charged, oil-in water, unpreserved ophthalmic emulsion that contains ciclosporin (CsA). Its formulation contains an excipient, cetalkonium chloride, which acts as a cationic agent and is specifically designed to prolong the time each eye drop stays on the epithelial layer of the eye. Ciclosporin has an anti-inflammatory effect on the cornea and the lacrimal (tear) gland. Following administration, ciclosporin blocks the expression of pro-inflammatory cytokines and subsequently enters corneal and conjunctival infiltrated T-cells, activating them. It has a marketing authorisation in the UK for treating ‘severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes’. Ciclosporin is administered as an eye drop of 1 mg/ml once daily at bed time.
- 2.2 The acquisition cost of a monthly course of ciclosporin is £72 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.
- 2.3 The most common adverse reactions with ciclosporin are eye pain, eye irritation, lacrimation, ocular hyperaemia and eyelid erythema.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

### **3 The company's submission**

The Appraisal Committee (section 9) considered evidence submitted by Santen Pharmaceutical and a review of this submission by the Evidence Review Group (ERG; section 10).

#### ***Clinical effectiveness***

- 3.1 The company identified 2 multicentre (including the UK) double-masked, randomised controlled clinical trials relevant to the decision problem, SANSIKA and SICCANOVE. These trials compared ciclosporin with a vehicle in people with dry eye disease that had not improved despite treatment with artificial tears.
- 3.2 SANSIKA (n=246) included patients with severe keratitis and severe dry eye disease defined as having a Corneal Fluorescein Score (CFS) of 4 on the modified Oxford scale, a Schirmer score (without anaesthesia) of 2 mm to 10 mm and an Ocular Surface Disease Index (OSDI) score of 23 or more. The trial compared ciclosporin in combination with artificial tears with the vehicle plus artificial tears. The vehicle contained the excipient cetalkonium chloride and patients were allowed to use preservative-free artificial tears as needed. SANSIKA was divided into 2 parts: part 1 studied the efficacy of ciclosporin over 6 months (n=245) and part 2, a 24-week open-label extension, assessed the long-term safety of ciclosporin up to 12 months (n=207). Randomisation was stratified by centre. Treatment compliance was measured by the number of used and unused containers of ciclosporin in relation to the duration of the follow-up interval.

- 3.3 SICCANOVE (n=492) included patients with moderate to severe dry eye disease defined as having a CFS of 2–4 on the modified Oxford scale, a Schirmer score (without anaesthesia) of 2 mm to 10 mm, a score of 4 or more on Lissamine green staining and a tear break-up time score of 8 seconds or less. Randomisation was stratified by Sjögren’s syndrome. Treatment compliance was measured by asking the patient or legal representative(s) about compliance with the dose regimen of ciclosporin (once daily at bedtime in both eyes). The vehicle used in the trial was benzalkonium chloride.
- 3.4 Both trials included study visits at months 0, 1, 3 and 6; in part 2 of SANSIKA, study visits also took place at months 9 and 12. The company noted that patient baseline characteristics were well balanced between treatment groups in both trials in terms of age, gender, Sjögren’s syndrome, CFS score, OSDI score and Schirmer test score.
- 3.5 The primary end points in SICCANOVE were change from baseline CFS score at month 6, measured using the modified Oxford grading scale, and change from baseline ocular discomfort at month 6, assessed using a global score (a mean of 8 individual symptoms: burning/stinging; itching; foreign body sensation; blurred vision; eye dryness; photophobia; pain and sticky feeling), measured on a visual analogue scale (VAS). A negative change from baseline indicated an improvement. In SANSIKA, the primary end point was change from baseline in CFS-OSDI, a composite variable combining the CFS and OSDI scores, at month 6. The definition of response using CFS-OSDI was:
- improvement of 2 points or more from baseline in CFS
  - improvement of 30% or more from baseline in OSDI.

Secondary end points were: change from baseline in CFS, ocular discomfort and CFS-OSDI analysed at other time points, use of concomitant artificial tears, investigator global evaluation of efficacy, Schirmer test (without anaesthesia) in both eyes, human leukocyte antigen-DR (HLA-DR) expression on the conjunctival cell surface by impression cytology, tear break-up time in both eyes, corneal and conjunctival staining assessed using the Van Bijsterveld grading system (Lissamine Green Staining), tear film osmolarity in both eyes, and quality of life measured with the EuroQoL 5D Questionnaire (EQ-5D) and the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25). Adverse events were separated into ocular and systemic adverse events.

3.6 In both trials, the efficacy end points were analysed based on the full analysis set (n=489 in SICCANOVE, n=245 in SANSIKA part 1 and n=207 in SANSIKA part 2), which included all patients who had any amount of study drug and for whom post-baseline data were available. Statistical significance was set at a significance level of 5% ( $p \leq 0.05$ ). The company used the last observation carried forward method for imputing missing values. The company also conducted different analyses for imputing missing data to check the influence of the method on the efficacy estimate. The analyses for the safety end points were based on the safety analysis set (n=492 in SICCANOVE, n=244 in SANSIKA part 1 and n=207 in SANSIKA part 2), which included all patients for whom there was evidence that they used the study medication. For the efficacy analyses, the interaction between treatment and Sjögren's condition was also investigated and considered to be significant at a significance level of 20%.

3.7 The company conducted post hoc subgroup analyses in people with more severe dry eye disease in SICCANOVE (CFS of 4) and

in people with CFS of 3 or more and OSDI score of 23 or more at baseline. For SANSIKA, the company carried out several post hoc subgroup analyses including of the primary efficacy end point CFS-OSDI response rate (setting CFS improvement at 3 grades instead of 2).

- 3.8 The company presented the results from SICCANOVE and SANSIKA for the primary end points. Results from SICCANOVE showed that there was a statistically significant reduction in CFS from baseline to month 6 with ciclosporin compared with the vehicle ( $p=0.009$ ). However, none of the results presented for the primary end point in SANSIKA was statistically significant. The company stated that there are many possible explanations for this, including the lack of correlation between signs and symptoms of dry eye disease and the possible beneficial effects of the vehicle itself.
- 3.9 The company presented an analysis of CFS score change from baseline over time in SANSIKA, which showed a statistically significant decrease in both treatment groups ( $p<0.001$ ). It noted that there was a statistically significant benefit with ciclosporin compared with the vehicle over the 6-month treatment period ( $p=0.017$ ). At 6 months, the decrease in CFS score from baseline was statistically significantly greater with ciclosporin than with the vehicle ( $p=0.037$ ).
- 3.10 From its post hoc analysis of CSF-OSDI in SANSIKA (using an improvement of 3 grades or more in CSF as criteria for improvement), the company noted that there was a statistically significantly higher response with ciclosporin (imputed data: 18.8%; observed data: 21.4%) compared with the vehicle (imputed data: 7.7%; observed data: 8.5%;  $p=0.016$  and  $p=0.012$  based on imputed and observed data respectively).



- 3.11 Results of HLA-DR in SANSIKA showed that at 6 months, ciclosporin was associated with a statistically significant decrease in HLA-DR from baseline compared with the vehicle ( $p=0.021$ ). This demonstrated that ciclosporin had an anti-inflammatory effect. The company noted that this is important because dry eye disease is characterised by inflammatory changes on the ocular surface.
- 3.12 The company presented the median use of artificial tears instead of the mean because the data distribution was skewed. It stated that there were no differences in the use of artificial tears between treatment groups during all visits in part 1 in SANSIKA but noted that the number of missing data was high. The company stated that considering all available data, there was a progressive decrease in the use of artificial tears over time in both treatment groups. The results in part 2 showed a steady decrease in the use of artificial tears during the first 6 months in both treatment groups ( $-3.8$  drops per day per eye in people who had ciclosporin in both parts of SANSIKA, and  $-2.6$  drops per day per eye in people who had the vehicle alone in part 1 and ciclosporin in part 2).
- 3.13 The company also analysed CFS-OSDI response rates in part 2 of SANSIKA. It noted that responses were similar in both treatment groups at months 9 and 12. At month 12, for people who had ciclosporin in both parts of SANSIKA, the response rate was 39.1%; for those who had the vehicle alone in part 1 and switched to ciclosporin in part 2, the response rate was 38.0%.
- 3.14 The company presented the health-related quality of life results from SANSIKA using the NEI-VFQ-25 and EQ-5D questionnaires. The results using NEI-VFQ-25 were similar between treatment groups at baseline and at 6 months but there was an increase in the mean NEI-VFQ-25 composite score over time in both treatment groups. There were no differences in the EQ-5D summary index

and the EQ-5D VAS score between baseline and at 6 months in both treatment groups, or between treatment groups. The company noted that the tariff used to estimate the health utility values was based on UK data from 1993 (Rabin et al, 2011).

3.15 The company presented the results of meta-analyses of SICCANOVE and SANSIKA for the composite end point CFS-OSDI response rate at 6 months for:

- all patients: 21.6% for ciclosporin compared with 13.1% for the vehicle (p=0.015)
- patients with severe dry eye disease: 29.5% for ciclosporin compared with 18.3% for the vehicle (p=0.038)
- patients with Sjögren's syndrome: 19.2% for ciclosporin compared with 11.6% for the vehicle (p=0.113)
- patients with Sjögren's syndrome and severe dry eye disease: 23.4% for ciclosporin compared with 9.4% for the vehicle (p=0.036).

3.16 The company presented pooled adverse effects results from SANSIKA and SICCANOVE. The company explained that treatment-emergent adverse effects represent any event occurring after the baseline visits, related or not to the study medication, whereas treatment-related adverse effects represent an event considered by the investigator to be related to the study medication. The most frequent treatment-emergent adverse effects with ciclosporin were instillation site pain, eye irritation, instillation site irritation and eye pain. The most frequent treatment-emergent adverse effects with the vehicle were eye pain, meibomianitis (an inflammation of the meibomian glands, a group of sebaceous glands in the eyelids) and reduced visual acuity. The company concluded that the observed adverse effects of ciclosporin were

mild to moderate and temporary and that overall ciclosporin is safe and well tolerated.

### ***Cost effectiveness***

- 3.17 The company presented a de novo Markov economic model that assessed the cost effectiveness of ciclosporin compared with standard care (artificial tears) in patients aged over 18 years with dry eye disease and severe keratitis whose disease had not adequately responded to tear substitutes. The company stated that the cost-effectiveness analysis was conducted from an NHS and Personal and Social Services perspective, costs and outcomes were discounted at 3.5% per year, the time horizon was 30 years and the cycle length was 3 months. The company noted that because patients in SANSIKA represent the licensed population, inputs in the model were derived from this trial where possible. Because the comparator in SANSIKA (vehicle, which contained the excipient cetalkonium chloride) is not commercially available and artificial tears represent established clinical practice in the NHS for this population, the company viewed the response or reduction in the use of artificial tears in the vehicle group as a regression to the mean. The baseline use of artificial tears in SANSIKA was assumed to be reflective of standard care in the NHS. The model included 7 different states: treatment induction, treatment responders, non-responders, temporary punctal plugs, permanent punctal plugs, post plugs and death. Patients were assumed to be aged 61 years, they could die at any time, and the model included equal numbers of men and women.
- 3.18 Treatment response was represented using the observed data from the post hoc analysis of CFS-OSDI response rate from part 1 of SANSIKA (defined as improvement of 3 points or more from baseline CFS and improvement of 30% or more from baseline

OSDI). Response rates from the vehicle group were used to derive response rates for the artificial tears group in the model. People whose disease responded to the 6-month induction period continued treatment until there was no response. These response rates were derived from part 2 of SANSIKA. Patients who had the vehicle in part 1 of SANSIKA and ciclosporin in part 2 were not included in the estimates for the model. The company assumed that transition probabilities were constant over time. The probability of stopping treatment with ciclosporin after 6 months (the end of SANSIKA) was taken from the rate of patients stopping treatment with ciclosporin between 6 and 12 months in part 2 of SANSIKA. For the artificial tears group, the rate of patients who stopped having the vehicle during part 1 of SANSIKA was used as a proxy for the estimates after the end of the trial. The annual rate of temporary punctal plugs was assumed to be 0.01 based on a study by Clegg (2006) and only 10% of people who had temporary punctal plugs were assumed to then have permanent punctal plugs. The response rate to permanent punctal plugs was assumed to be 100%. Patients with temporary or permanent punctal plugs were assumed to not use artificial tears. Mortality rates were derived from the general population aged 61 years, which was the mean age of patients in SANSIKA.

- 3.19 The composition of preservative-free artificial tears was polyvinyl alcohol, carbomers and paraffin. The company assumed that administration, monitoring and testing costs with ciclosporin or artificial tears were zero, because all treatments were self-administered and it was assumed that the rate of ophthalmologist visits, tests and monitoring were similar in both treatment groups irrespective of the response status of the disease. It was assumed that people with severe dry eye disease have treatment in both eyes. The company assumed that the average number of drops per

eye per day at baseline was similar in both treatment groups as in SANSIKA. The company incorporated the change in artificial tear use at 6 months to the ciclosporin and artificial tears groups in SANSIKA in the model, noting that the vehicle could have had an effect on the reduction of artificial tears use in the comparator group. For patients whose disease did not respond to treatment, the number of artificial tears per eye per day was similar to this use at baseline. Because treatment-related adverse effects were of low severity and transient, these were not included in the model other than through a reduction in the treatment continuation rates. The source of the costs for punctal plugs was NHS Reference Costs 2013. Unit costs were taken from the British National Formulary (month not stated).

- 3.20 The company used utility data from SANSIKA in the model (utility for response: 0.74; utility for no response: 0.66). It noted that patients whose disease responds need fewer artificial tears and have a higher utility, which was assumed to be constant during response. Patients with punctal plugs had the same utility as patients whose disease responds with ciclosporin or artificial tears.
- 3.21 The company's cost-effectiveness analysis produced an incremental cost-effectiveness ratio (ICER) for ciclosporin plus artificial tears compared with vehicle plus artificial tears of £19,156 per quality-adjusted life year (QALY) gained, with an associated incremental cost of £713 and 0.037 additional QALYs.
- 3.22 The company conducted deterministic and probabilistic sensitivity analyses, which showed that varying the utility value for responders had the largest effect on the ICER. When varying the utility value for responders between 0.67 and 0.81, the ICER for ciclosporin plus artificial tears compared with artificial tears alone ranged from £165,654 to £10,166 per QALY gained. Other variables that had a

notable effect on the ICER were the acquisition cost of ciclosporin and the response probabilities to ciclosporin and the vehicle at 6 months. The probabilistic analysis results gave an ICER of £18,835 per QALY gained for ciclosporin plus artificial tears compared with vehicle plus artificial tears. The company noted that ciclosporin had a probability of 46.4% to be considered a cost-effective use of NHS resources at a maximum acceptable ICER of £20,000 per QALY gained. It also noted that a number of simulations were associated with incremental benefits close to zero, meaning that the probabilistic results should be interpreted with caution.

3.23 The company presented results from several scenario analyses including:

- using the primary end point definition for CFS-OSDI from SANSIKA (that is, improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI): ICER for ciclosporin plus artificial tears compared with artificial tears alone, £19,156 per QALY gained
- using utility values from Schiffman et al. (0.72 for non-responders and 0.78 for responders): ICER for ciclosporin plus artificial tears compared with artificial tears alone, £33,291 per QALY gained
- varying the time horizon (showing that the ICER increases above £20,000 per QALY gained when the time horizon is less than 10 years)
- assuming that only 1 eye is treated: ICER for ciclosporin plus artificial tears compared with artificial tears alone, £23,290 per QALY gained.

- 3.24 The company did not present a subgroup analysis for patients with Sjögren's syndrome. It noted that SANSIKA was not powered to assess the benefit of ciclosporin in this subgroup, and any inference would have meant using published literature in different patient groups or clinical input which would have added uncertainty to the model.

***ERG comments***

- 3.25 The ERG noted that only 17% of patients included in SICCANOVE had severe dry eye disease (as per the definition used in SANSIKA), and that the company presented post hoc analyses for them. The ERG considered that these post hoc analyses were appropriately used to inform pre-specified analyses in SANSIKA and agreed with the company that evidence from SANSIKA is more relevant to the decision problem.
- 3.26 The ERG considered that the value of the evidence from SANSIKA is limited because the comparator is the ciclosporin vehicle, rather than any of the comparators specified in the NICE scope. The ERG noted that the vehicle is not commercially available and it is not currently used in routine clinical practice. The ERG considered that the improvements seen in the comparator group in the trial may be because of the vehicle itself, concomitant use of artificial tears or both. The ERG considered that the relevant comparator for ciclosporin was actually other ciclosporin formulations currently used in clinical practice in England. However, the ERG noted that because there are no trials comparing ciclosporin with other pharmaceutical formulations, combined with the absence of a common comparator and the differences in vehicles used in each formulation, a robust indirect comparison was not possible.

- 3.27 The ERG highlighted that whereas there was no restriction in concomitant artificial tear use in SANSIKA, SICCANOVE restricted this to a maximum of 6 drops per day. The ERG also noted that it is unclear whether the vehicle used in SANSIKA (cetalkonium chloride) should be considered similar to that used in SICCANOVE (benzalkonium chloride). The ERG noted that the rate of some adverse effects (eye irritation, eye pain, site irritation and site pain) was different between these trials and considered that this may be because of differences in the excipients.
- 3.28 The ERG commented on the clinical relevance of the composite primary end point in SANSIKA (CFS-OSDI response defined as improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline in OSDI). It noted that both CFS and OSDI are recognised and validated outcomes to measure signs and symptoms respectively, but was concerned that the validity of the composite end point is unknown. The ERG stated that it is unclear whether CFS-OSDI response is a clinically relevant end point and what the response thresholds should be to define a response. It also noted that the response thresholds would depend on the criteria used for defining severe dry eye disease.
- 3.29 The ERG noted that the pooled adverse effects data for SICCANOVE and SANSIKA presented by the company included an estimate for the relative risk between treatment groups, implying that statistical analyses were conducted. The ERG stated that although pooling adverse effects data is normally the preferred method for reporting the adverse effects results, only SANSIKA included patients with severe dry eye disease exclusively and different vehicles were used in SANSIKA and SICCANOVE. It therefore considered the results of SANSIKA to be of greater importance for the appraisal. The ERG also noted that there were



some differences in the rates of adverse effects between SANSIKA and SICCANOVE, and considered that these differences may be because of the use of different vehicles or differences in disease severity between the 2 trials.

- 3.30 The ERG considered that results from SANSIKA could not be used directly to inform an economic evaluation because the comparator (vehicle) is not commercially available and is not currently used in routine clinical practice (which the ERG considered to be other ciclosporin formulations). However, because of the lack of data, it noted that the only valid economic comparison would be a cost-minimisation analysis assuming that all ciclosporin-based treatments have equivalent efficacy, similar adverse effects and similar administration, prescribing and monitoring costs. The ERG considered that there was no sufficient evidence available to support a cost-effectiveness analysis of ciclosporin compared with established clinical practice in the NHS for severe dry eye disease. Although the ERG provided further critique on the company's economic model, it highlighted that this should not be understood as any expression of support for the validity of the model or the results obtained from it.
- 3.31 The ERG noted that there were more women (85.3%) than men in SANSIKA and that the age range at baseline was wide (22 to 87 years). The ERG considered that it would be more appropriate to carry out modelling for each age and gender group, combining the results to obtain a weighted average result. Having done this, the resulting ICER for ciclosporin plus artificial tears compared with vehicle plus artificial tears was £19,382 per QALY gained when using the post hoc CFS-OSDI definition of response from SANSIKA, and £33,625 per QALY gained when using the trial CFS-OSDI definition of response from SANSISKA.

- 3.32 The ERG noted that the company used the post hoc definition of CFS-OSDI response from SANSIKA, which is more restrictive than the trial definition. It stated that this had a large effect on the cost-effectiveness results because it excluded the level of benefit that most favoured the vehicle group.
- 3.33 The ERG highlighted the population heterogeneity in the company's model. It noted that approximately 10% of patients in SANSIKA were diagnosed less than 2 years before randomisation and that there was no statistically significant difference in CFS-OSDI response from baseline at 6 months in the ciclosporin group using either the pre-specified ( $p=0.41$ ) or the post hoc ( $p=0.98$ ) definition of response. However, it noted that patients who had vehicle and were diagnosed less than 2 years before randomisation showed CFS-OSDI response rates nearly double those in patients having ciclosporin. The ERG cautioned that there were too few patients in this analysis to derive definite conclusions but suggested that patients who were more recently diagnosed may show short-term improvements in their condition, delaying the need for treatments such as ciclosporin.
- 3.34 The ERG noted that the company applied probabilities for continuing treatment beyond the end of the trial from different time periods for each treatment group (6–12 months for ciclosporin and 0–6 months for the vehicle), indicating lower discontinuation rates in the ciclosporin group (10.9%) than in the vehicle group (12.2%). However, it also noted that Kaplan–Meier analyses in SANSIKA showed that there was a higher rate of stopping treatment in the ciclosporin group during the first month remaining stable thereafter (5.9% per 3 months) and that rates of stopping treatment were lower in the vehicle group with no evidence of any initial excess of people stopping treatment (4.6% per 3 months). The ERG applied

these rates in scenario analyses and noted that this was its preferred option for modelling stopping treatment rates. The results increased the ICER of ciclosporin plus artificial tears compared with vehicle plus artificial tears to £25,020 per QALY gained when using the post hoc CSF-OSDI definition of response, and to £133,290 per QALY gained when using the trial definition of response.

- 3.35 The ERG found an inconsistency between the company's calculation of artificial tear use at baseline and at 6 months. The ERG considered that no differences in artificial tear use between treatment groups should be included in the model at baseline and at 6 months because neither of these differences was statistically significant. The ERG applied an average use of 6.83 drops per eye per day to both treatment groups in the model in scenario analyses, which produced ICERs for ciclosporin plus artificial tears compared with vehicle plus artificial tears of £20,950 per QALY gained when using the post hoc CFS-OSDI definition of response, and £36,307 per QALY gained when using the trial CFS-OSDI definition of response.
- 3.36 The ERG also noted that the company applied treatment costs in the first 6 months assuming that treatment is prescribed for 3 months at the beginning of each cycle. It considered that this does not take into account the small risk of patients dying or stopping treatment during a 3-month cycle. Based on clinical advice, the ERG assumed that treatment was prescribed monthly in its scenario analyses. These produced ICERs for ciclosporin plus artificial tears compared with vehicle plus artificial tears of £21,916 per QALY gained when using the post hoc CSF-OSDI definition of response, and £35,915 per QALY gained when using the trial CFS-OSDI definition of response.

- 3.37 The ERG noted that the company's approach to modelling the utility values based on response is not influenced by treatment because EQ-5D results are pooled across both treatment groups. The ERG examined the EQ-5D results and noted that patients in the vehicle group showed a larger utility benefit based on response compared with patients in the ciclosporin group (+0.038 using the trial definition of response, or +0.049 using the post hoc definition). The ERG stated that pooling utility values in the model by response eliminated the potential effect of any differences because of treatment. The ERG considered that the most likely reason for the observed differences in utility values between treatments was that the additional adverse effects in patients having ciclosporin reduced the advantages derived from a response to treatment. The ERG investigated the effect of using separate trial utility values for each treatment group in scenario analyses, and obtained an ICER for ciclosporin plus artificial tears compared with vehicle plus artificial tears of £24,473 per QALY gained when using the post hoc CSF-OSDI definition of response. When using the trial CFS-OSDI definition of response, ciclosporin plus artificial tears was dominated by vehicle plus artificial tears (that is, was more expensive and less effective than vehicle plus artificial tears).
- 3.38 Cumulatively applying the ERG's changes to the company's model (in terms of age-gender modelling, stopping treatment, treatment costs, responder utilities by treatment group, artificial tear use and a small amendment in discounting) produced an ICER of £53,378 per QALY gained for ciclosporin plus artificial tears compared with vehicle plus artificial tears when using the post hoc CFS-OSDI definition of response. When using the trial CFS-OSDI definition of response, the cumulative effect of these amendments resulted in ciclosporin being dominated by vehicle plus artificial tears.

- 3.39 The ERG carried out an exploratory cost-minimisation analysis comparing ciclosporin with other pharmaceutical formulations of ciclosporin. The results showed that ciclosporin (Ikervis) is less costly (£72 monthly) than Restasis (£119.75 monthly) but more costly than the other 2 ciclosporin formulations currently used in clinical practice in the NHS (Optimmune 0.2% CsA ointment: £55.24 monthly; 2% CsA drops: £47.24 monthly).
- 3.40 Full details of all the evidence are in the [Committee papers](#).

## **4 Consideration of the evidence**

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ciclosporin, having considered evidence on the nature of dry eye disease and the value placed on the benefits of ciclosporin by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The Committee discussed the current clinical management of severe dry eye disease in the NHS. It heard from the clinical experts that treatment depends on the severity of the disease. The clinical experts noted that in England, people with severe dry eye disease use several drops of artificial tears per day. If the disease does not respond to artificial tears, treatment with other individually prepared ciclosporin formulations and corticosteroids are considered. The clinical experts explained that because of the inflammatory nature of the disease, treatment with corticosteroids is given initially because of their rapid effect on reducing inflammation. They noted that treatment with corticosteroids is often stopped after 6–8 weeks because of their associated adverse effects. The clinical experts stated that ciclosporin is sometimes started at the same time as steroid treatment because ciclosporin

has a slower onset of action and it will start to show an effect by the time steroid treatment is stopped. They also noted that treatment with corticosteroids can be restarted again if needed. The clinical experts explained that corticosteroids would be considered as an additional treatment to ciclosporin if needed and that they have the effect of allowing people to continue treatment with ciclosporin for longer. The clinical experts also noted that punctal plugs remain an option for people with severe dry eye disease that does not respond to artificial tears and would be considered after treatment with ciclosporin. The Committee understood that the appropriate place for ciclosporin in the treatment pathway was for severe dry eye disease that has not improved despite treatment with artificial tears, in line with its marketing authorisation. The Committee also understood that in clinical practice ciclosporin would be given in combination with corticosteroids (if needed) and artificial tears, and concluded that this represents established clinical practice without ciclosporin, that is, the definition of the comparator in the final NICE scope.

- 4.2 The Committee considered other commercially available ciclosporin formulations noting that they were not included as comparators in the final NICE scope. The clinical experts explained that there are 3 different ciclosporin formulations, some of which are being used in the NHS: Restasis, which has marketing authorisation in the US but does not have a marketing authorisation in the UK; Optimune, which does not have a marketing authorisation in the UK for human use but is licensed for veterinary use; and 2% ciclosporin (CsA) eye drops which does not have a marketing authorisation in the UK. They noted that Restasis is more expensive than ciclosporin (Ikervis) and is not used in the UK. A clinical expert highlighted that 2% CsA eye drops are not widely used in the NHS for people with severe dry eye disease because of the high concentration and

associated severe side effects. The clinical experts also noted that Optimune ointment is more widely used in the NHS for people with severe dry eye disease but that many people are not willing to have treatment because of its veterinary marketing authorisation. The clinical experts also noted that it can only be used at night because it causes blurred vision and that there are some people who cannot tolerate ointments. The Committee heard from the company and the ERG that any comparison of ciclosporin (Ikervis) with other ciclosporin formulations would not be robust and would be subject to a high degree of uncertainty because of the lack of clinical evidence comparing these treatments. The Committee agreed that it would have liked to have seen a scenario analysis comparing ciclosporin (Ikervis) with other ciclosporin formulations, but it noted that the costs of these other ciclosporin formulations were not greatly different from that of ciclosporin (Ikervis). In summary, the Committee considered it acceptable that these ciclosporin formulations were not used as comparators for its decision-making.

### ***Clinical effectiveness***

- 4.3 The Committee discussed the clinical effectiveness evidence for ciclosporin. It noted that the company and the ERG considered SANSIKA to be more relevant than SICCANOVE because SICCANOVE included people with moderate to severe dry eye disease and SANSIKA only included people with severe dry eye disease. The Committee noted that ciclosporin has a marketing authorisation in the UK for treating severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes. Therefore, it concluded that SANSIKA was more relevant than SICCANOVE for its decision-making.

4.4 The Committee discussed the use of the vehicle as a comparator in the trials. The Committee heard from the company that ciclosporin contains the active ingredient ciclosporin and the excipient (cetalkonium chloride), whereas the vehicle only contains the excipient. The Committee heard from the clinical experts that the excipient is used to help the ciclosporin eye drop stay on the eye surface for longer. Both the company and the ERG stated that the vehicle may have some beneficial effects on its own, which could affect the relative clinical effectiveness of ciclosporin plus artificial tears compared with the vehicle plus artificial tears. The Committee heard from the clinical experts that the vehicle alone is not commercially available as a treatment although the formulation used in ciclosporin (Ikervis) is similar to an artificial tear (Cationorm), but which is also not available in the UK. The Committee considered that it was possible that the vehicle could have had an effect on the relative results of the clinical trials and that its use as a comparator in the trials limited the interpretation of the results. It also considered that the appropriate comparison should have been ciclosporin plus corticosteroids (if needed) and artificial tears compared with corticosteroids (if needed) and artificial tears and that it would have liked to have seen an indirect comparison for this. The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice.

4.5 The Committee considered the primary end point in SANSIKA, namely Corneal Fluorescein Staining score – Oxford Surface Disease Index (CFS-OSDI) response, which was a composite outcome of individual measures for signs (CFS) and symptoms (OSDI). It heard from the clinical experts that there is no established and standardised measure of response in severe dry eye disease and that several measures of signs and symptoms are



used in clinical practice in the NHS, including both CFS and OSDI. The Committee noted that in SANSIKA, ciclosporin plus artificial tears did not show a statistically significant difference compared with the vehicle plus artificial tears in CFS-OSDI response rate, and that the only statistically significant difference between ciclosporin plus artificial tears and the vehicle plus artificial tears was shown in changes in CFS over time and in human leukocyte antigen-DR (HLA-DR). The Committee noted that ciclosporin plus artificial tears did not show any differences compared with the vehicle plus artificial tears in any measure for symptoms. It heard from the company that this could be because of the well-known poor correlation between signs and symptoms and because of the possible beneficial effect of the vehicle on its own. The Committee noted that, based on the evidence presented, ciclosporin had not shown superior clinical effectiveness to the vehicle. It then discussed each of these issues separately.

- 4.6 The Committee considered comments from the clinical experts that severe dry eye disease is an inflammatory disease associated with long-term disease progression. The clinical experts also stated that people with severe dry eye disease are close to having complete corneal blindness and that any treatment which offers a benefit in terms of reducing inflammation should be considered clinically relevant. The clinical experts explained that improvements in signs of dry eye disease will generally translate into benefits in symptoms in the long term. The Committee noted that ciclosporin showed a statistically significant difference in reducing HLA-DR, a measure of inflammation, and in change in CFS, a measure of corneal damage, and concluded that these outcomes were clinically relevant.

- 4.7 The Committee discussed the company's post hoc analyses for SANSIKA. In particular, it considered the results from the post hoc analysis for the primary end point CFS-OSDI response, for which the company adopted a more stringent definition of response (improvement in CFS score of 3 or more). The Committee noted that ciclosporin showed statistically significant differences compared with the vehicle alone in this post hoc analysis. However, it was aware that the ERG considered that the clinical relevance of this revised definition of response was unclear and that it excluded the level of benefit which most favoured the vehicle group. The clinical experts stated that in clinical practice there is no clear definition for response and non-response, but that the greater the benefit in CFS the more likely this would have a beneficial effect in slowing disease progression. The Committee had reservations about all the post hoc analyses presented by the company and considered that these analyses were not robust enough to reach a conclusion on the relative clinical effectiveness of ciclosporin compared with the vehicle.
- 4.8 The Committee discussed the results of the company's meta-analysis for the subgroup of people with Sjögren's syndrome and severe dry eye disease. It heard from the clinical experts that people with Sjögren's syndrome and severe dry eye disease have a lifelong disease which is difficult to treat and needs careful management. The clinical experts stated that because dry eye disease was associated with other autoimmune diseases including Sjögren's syndrome, this subgroup was clinically relevant and it would benefit most from treatment with ciclosporin. The Committee noted that the results of the meta-analysis showed that the CFS-OSDI response rate at month 6 was statistically significantly higher with ciclosporin plus artificial tears compared with the vehicle plus artificial tears and that, although the numbers of patients included

in the analysis was small, this subgroup was clinically relevant. The Committee concluded that ciclosporin plus artificial tears appeared to show greater benefits compared with the vehicle plus artificial tears in the subgroup of people with Sjögren's syndrome and severe dry eye disease.

### ***Cost effectiveness***

- 4.9 The Committee considered the cost-effectiveness evidence presented by the company for ciclosporin plus artificial tears compared with artificial tears alone. It noted that the company used the results from the vehicle group in SANSIKA as a proxy to model the results of artificial tears alone and that the company stated that the response or reduction in the use of artificial tears in the vehicle group was viewed as a regression to the mean. The Committee noted the ERG's concerns highlighting that the SANSIKA results could not be used directly to inform an economic evaluation because the comparator in the model was the vehicle. The Committee concluded that the company's model was of limited relevance because it failed to show the cost effectiveness of ciclosporin compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears.
- 4.10 The Committee noted that the company used the post hoc analysis for CFS-OSDI response in its base-case analysis, in which ciclosporin showed a statistically significantly higher response than the vehicle and which excluded the level of benefit that most favoured the vehicle group. The Committee was aware that when using the original CFS-OSDI response data, the incremental cost-effectiveness ratio (ICER) for ciclosporin plus artificial tears compared with vehicle plus artificial tears increased substantially. The Committee restated its concerns about the company's post hoc analyses of SANSIKA and concluded it was more appropriate to

use the original CFS-OSDI response data in the model (see section 4.7).

4.11 The Committee considered the ERG's concerns about how stopping treatment had been modelled in the company's base-case analysis. The Committee noted that the company had used the probabilities for continuing treatment beyond the end of the trial from different time periods for each treatment group (6–12 months for ciclosporin and 0–6 months for the vehicle). It heard from the ERG that it considered it to be more appropriate to use Kaplan–Meier analyses for time to stopping treatment, which accurately take into account the moment when the patient stopped treatment. The Committee was aware that when using the ERG's approach, there was a higher rate of people stopping treatment in the ciclosporin group during the first month and this number subsequently remained stable, whereas the rates of people stopping treatment were lower in the vehicle group with no evidence of an initial higher rate of people stopping treatment. The ERG suggested that this could be related to a higher rate of people stopping treatment with ciclosporin because of adverse effects. The Committee heard from the clinical experts that in clinical practice treatment is not stopped because of adverse effects. However the ERG stated that in the trials, the majority of people who stopped treatment did so because of treatment-related adverse effects. The clinical experts explained that because ciclosporin is given with intermittent treatment with corticosteroids in clinical practice, the rates of stopping treatment were expected to be lower than in the trial where corticosteroids were not used, because corticosteroids allow treatment with ciclosporin to be given for longer. The Committee was aware that this was a parameter that had a large effect on the ICER for ciclosporin plus artificial tears compared with vehicle plus artificial tears and it considered whether the ICER

would be different if corticosteroids were given with ciclosporin (and so ciclosporin would not be stopped). It heard from the ERG that in this scenario the ICER for ciclosporin plus artificial tears compared with vehicle plus artificial tears was likely to decrease, but noted that it was not possible to derive definite conclusions because the company had not presented a model including treatment with corticosteroids. The Committee concluded that to inform its decision-making, it would like to see a model for ciclosporin plus corticosteroids (if needed) and artificial tears compared with corticosteroids (if needed) and artificial tears alone which accurately captures stopping rates with ciclosporin and in which the ERG's approach to stopping treatment is applied.

- 4.12 The Committee discussed the utility values used in the model. It noted that the company used pooled EuroQoL 5D questionnaire (EQ-5D) data from SANSIKA for both response and non-response. However, in its exploratory analyses the ERG applied different utility values for response by treatment and people in the vehicle group showed a larger utility benefit based on response compared with people in the ciclosporin group. The ERG suggested that the differences in utility values between treatments could be because of the additional adverse effects in people having ciclosporin. The Committee heard from the clinical experts that in clinical practice, adverse events were mild and transient and would not have an effect on quality of life. The ERG noted that adverse effects such as instillation site irritation were likely to occur at each instillation and these adverse effects had not been captured anywhere in the model. The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life and if different utility values depending on treatment should be included in the model. It recognised that the utility value for response was the parameter that had the biggest effect on the ICER and that assuming different

utility values for response by treatment group led to ciclosporin plus artificial tears being dominated by vehicle plus artificial tears (that is, it was both more expensive and less effective). The Committee concluded that it would like to see a sensitivity analysis using different utility values for response by treatment in the model for ciclosporin plus corticosteroids (if needed) and artificial tears compared with corticosteroids (if needed) and artificial tears alone.

4.13 The Committee discussed the use of resources and costs included in the model. It heard from the clinical experts that the company's assumption that people who have temporary or permanent punctal plugs do not use artificial tears was implausible and did not reflect clinical practice. The Committee also noted that the ERG considered the way in which the company modelled the use of artificial tears at 6 months to be inconsistent with the company's own approach for modelling the use of artificial tears at baseline. The ERG stated that because there were no statistically significant differences between treatment groups in the use of artificial tears at baseline or at 6 months, an average number of drops of artificial tears per day should be assumed for both treatment groups at 6 months consistent with the company's approach at baseline. The Committee also agreed with the ERG that ciclosporin should be assumed to be dispensed monthly (instead of 3 monthly). The Committee concluded that the model should incorporate amendments in the use of resources and costs reflecting that:

- that artificial tears may be used alongside punctal plugs
- both a baseline average and a 6-month average for the number of artificial tear drops used per day, for both treatment groups
- ciclosporin is dispensed and costs are incurred monthly.

- 4.14 The Committee noted that in its cost-effectiveness analyses, the company did not present a subgroup analysis for people with Sjögren's syndrome and severe dry eye disease. The Committee was aware that the clinical experts highlighted that people with Sjögren's syndrome and severe dry eye disease would be most likely to benefit from treatment with ciclosporin (see section 4.8). It concluded that a subgroup analysis of people with Sjögren's syndrome and severe dry eye disease should be provided as part of the cost-effectiveness analyses.
- 4.15 The Committee discussed the ERG's cost-minimisation analysis comparing ciclosporin (Ikervis) with the other ciclosporin formulations. It noted that ciclosporin (Ikervis) was less expensive than Restasis and that there was not a big cost difference compared with the other ciclosporin formulations. The Committee understood that the additional cost of ciclosporin (Ikervis) compared with Optimune ointment and 2% CsA eye drops could be explained by the additional cost of research and marketing authorisation. The Committee concluded that the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations and restated its previous consideration that it would have liked to have seen a scenario analysis comparing ciclosporin (Ikervis) with other ciclosporin formulations. It acknowledged, however, that these ciclosporin formulations were not included as comparators in the final NICE scope and concluded that it was acceptable that these formulations were not used as comparators for its decision-making (see section 4.2).
- 4.16 The Committee discussed the cost-effectiveness results of the company's model (see sections 3.21 – 3.23) and the ERG's subsequent amendments (see section 3.38). It considered that because it had not been presented with a model which compared

ciclosporin with established clinical practice, the results lacked relevance and the Committee concluded that it needed additional analyses to inform its decision-making. Therefore, the Committee was minded not to recommend ciclosporin for treating severe keratitis in adults with dry eye disease that has not improved despite treatment with artificial tears. The Committee requested further analyses from the company that addresses the issues identified (see sections 4.4 and 4.9–4.14), and which should be made available for the second Appraisal Committee meeting. These analyses should include:

- An indirect comparison of the clinical effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, and that of corticosteroids (if needed) and artificial tears.
- An economic model comparing the cost effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, with that of corticosteroids (if needed) and artificial tears. This cost effectiveness analysis should include:
  - the original SANSIKA Corneal Fluorescein Staining – Ocular Surface Disease Index (CFS-OSDI) definition of response (that is, improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI)
  - an evidence-based treatment stopping rates with ciclosporin plus corticosteroids (if needed) and artificial tears
  - changes to resource use and costs reflecting:
    - ◇ that artificial tears may be used alongside punctal plugs
    - ◇ both a baseline average and a 6-month average for the number of artificial tear drops used per day, for both treatment groups
    - ◇ the assumption that ciclosporin is dispensed and costs are incurred monthly



- sensitivity analyses using different utility values for response by treatment group
- a subgroup analysis for people with Sjögren’s syndrome and severe dry eye disease.

4.17 The Committee discussed the innovative nature of ciclosporin. The Committee noted that ciclosporin was not a novel technology, but it heard from the clinical experts that because people with severe dry eye disease were close to complete corneal blindness and there were no other effective treatments available and licensed in the UK, there was a high unmet medical need. The Committee also noted that this was even more important for people with severe dry eye disease and Sjögren’s syndrome because of the need for long-term management of the condition with an effective treatment that would help to delay disease progression. The company highlighted that ciclosporin was particularly beneficial because it is administered as 1 eye drop per day compared with other treatments that need to be provided several times per day. The company stated that the benefits in terms of administration had not been appropriately captured in the quality-adjusted life year (QALY) calculation. The Committee also noted that the use of several artificial tears per day can have a detrimental impact on quality of life and that the fact that ciclosporin helps to reduce the number of artificial tears needed was particularly important to patients. The Committee concluded that even though ciclosporin is used for treating severe dry eye disease which has not improved despite treatment with artificial tears in people who have a high unmet need, the new formulation of ciclosporin could not be considered an innovative technology.

**Summary of Appraisal Committee’s key conclusions**

TAXXX	Appraisal title: Ciclosporin for treating dry eye disease which has not improved despite treatment with artificial tears	Section
<b>Key conclusion</b>		
<p>The Committee is minded not to recommend ciclosporin within its marketing authorisation, that is, for treating severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.</p>		1.1
<p>The Committee recommends that NICE requests further analyses from the company, which should be made available for the second Appraisal Committee meeting, and should include:</p> <ul style="list-style-type: none"> <li>• An indirect comparison of the clinical effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, and that of corticosteroids (if needed) and artificial tears.</li> <li>• An economic model comparing the cost effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, with that of corticosteroids (if needed) and artificial tears. This cost effectiveness analysis should include: <ul style="list-style-type: none"> <li>– the original SANSIKA Corneal Fluorescein Staining – Ocular Surface Disease Index (CFS-OSDI) definition of response (that is, improvement of 2 points or more from baseline CFS and improvement of 30% or more from baseline OSDI)</li> <li>– an evidence-based treatment stopping rates with ciclosporin plus corticosteroids (if needed) and</li> </ul> </li> </ul>		1.2



	treatment with other individually prepared ciclosporin formulations and corticosteroids are considered.	
<b>The technology</b>		
Proposed benefits of the technology  How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	<p>The Committee heard from the clinical experts that because people with severe dry eye disease were close to complete corneal blindness and there were no other effective treatments available and licensed in the UK, there was a high unmet medical need.</p> <p>The company highlighted that ciclosporin was particularly beneficial because it is administered as 1 eye drop per day compared with other treatments that need to be provided several times per day.</p> <p>The Committee concluded that even though ciclosporin is used for treating severe dry eye disease which has not improved despite treatment with artificial tears in people who have a high unmet need, the new formulation of ciclosporin could not be considered an innovative technology.</p>	4.17
What is the position of the treatment in the pathway of care for the condition?	The Committee understood that the appropriate place for ciclosporin in the treatment pathway was for severe dry eye disease that has not improved despite treatment with artificial tears, in line with its	4.1

	marketing authorisation.	
Adverse reactions	The most common adverse reactions with ciclosporin are eye pain, eye irritation, lacrimation, ocular hyperaemia and eyelid erythema.	2.3
	The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life.	4.12
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee discussed the clinical effectiveness evidence for ciclosporin. It noted that the company and the ERG considered SANSIKA to be more relevant than SICCANOVE because SICCANOVE included people with moderate to severe dry eye disease and SANSIKA only included people with severe dry eye disease. The Committee concluded that SANSIKA was more relevant than SICCANOVE for its decision-making.	4.3
Relevance to general clinical practice in the NHS	The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice.	4.4
Uncertainties generated by the evidence	The Committee noted that ciclosporin plus artificial tears did not show any differences compared with the vehicle plus artificial tears in any measure for symptoms. It heard from	4.5

	<p>the company that this could be because of the well-known poor correlation between signs and symptoms and because of the possible beneficial effect of the vehicle on its own.</p> <p>The Committee noted that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice.</p> <p>The Committee had reservations about all the post hoc analyses presented by the company and considered that these analyses were not robust enough to reach a conclusion on the relative clinical effectiveness of ciclosporin compared with the vehicle.</p>	<p>4.4</p> <p>4.7</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The Committee concluded that ciclosporin plus artificial tears appeared to show greater benefits compared with the vehicle plus artificial tears in the subgroup of people with Sjögren’s syndrome and severe dry eye disease.</p>	<p>4.8</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice.</p> <p>The Committee noted that, based on the evidence presented, ciclosporin had not shown superior clinical effectiveness to the</p>	<p>4.4</p> <p>4.5</p>

	vehicle.	
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The Committee considered the cost-effectiveness evidence presented by the company for ciclosporin plus artificial tears compared with artificial tears alone. It noted that the company used the results from the vehicle group in SANSIKA as a proxy to model the results of artificial tears alone and that the company stated that the response or reduction in the use of artificial tears in the vehicle group was viewed as a regression to the mean.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee concluded that the company's model was of limited relevance because it failed to show the cost effectiveness of ciclosporin compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears.	4.9
	The Committee restated its concerns about the company's post hoc analyses of SANSIKA and concluded it was more appropriate to use the original CFS-OSDI response data in the model.	4.10
	The Committee concluded that to inform its decision-making, it would like to see a model for ciclosporin plus corticosteroids (if needed) and artificial tears compared with	4.11

	<p>corticosteroids (if needed) and artificial tears alone which accurately captures stopping rates with ciclosporin and in which the ERG’s approach to stopping treatment is applied.</p> <p>The Committee remained uncertain whether adverse effects would have a long-term effect on quality of life and if different utility values depending on treatment should be included in the model.</p> <p>The Committee heard from the clinical experts that the company’s assumption that people who have temporary or permanent punctal plugs do not use artificial tears was implausible and did not reflect clinical practice. The Committee also noted that the ERG considered the way in which the company modelled the use of artificial tears at 6 months to be inconsistent with the company’s own approach for modelling the use of artificial tears at baseline. The Committee also agreed with the ERG that ciclosporin should be assumed to be dispensed monthly (instead of 3 monthly).</p>	<p>4.12</p> <p>4.13</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential</p>	<p>The Committee noted that the company used pooled EuroQoL 5D questionnaire (EQ-5D) data from SANSIKA for both response and non-response. The Committee concluded that it would like to see a sensitivity analysis using different utility values for response by</p>	<p>4.12</p>



<p>significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>treatment in the model for ciclosporin plus corticosteroids (if needed) and artificial tears compared with corticosteroids (if needed) and artificial tears alone.</p> <p>The company highlighted that ciclosporin was particularly beneficial because it is administered as 1 eye drop per day compared with other treatments that need to be provided several times per day. The company stated that the benefits in terms of administration had not been appropriately captured in the quality-adjusted life year (QALY) calculation.</p>	<p align="center">4.17</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee concluded that a subgroup analysis of people with Sjögren’s syndrome and severe dry eye disease should be provided as part of the cost-effectiveness analyses for ciclosporin plus corticosteroids (if needed) and artificial tears compared with corticosteroids (if needed) and artificial tears alone.</p>	<p align="center">4.14</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee recognised that the utility value for response was the parameter that had the biggest effect on the ICER.</p>	<p align="center">4.12</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered that because it had not been presented with a model which compared ciclosporin with established clinical practice, the results lacked relevance and concluded that it needed additional analyses</p>	<p align="center">4.16</p>

	to inform its decision-making.	
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	<p>A professional group noted that if ciclosporin is not recommended by NICE in this guidance, a circumstance of postcode lottery may arise as the treatment (in the form of different pharmaceutical formulations) is currently being used in the UK.</p> <p>NICE had a referral from the Department of Health to appraise ciclosporin (Ikervis). Any recommendations can only be focused on the technology under appraisal and within the boundaries of its marketing authorisation. Therefore the availability of other formulations of ciclosporin was not considered to be an equality issue that could be addressed by the Committee because it is outside the remit of NICE technology appraisal guidance.</p>	

## 5 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

**Published**

- NICE Clinical Knowledge Summary for [dry eye syndrome](#) (2012).

## **6 Proposed date for review of guidance**

- 6.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens  
Chair, Appraisal Committee  
June 2015

## **7 Appraisal Committee members, guideline representatives and NICE project team**

### ***Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Professor Andrew Stevens**

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

#### **Professor Eugene Milne**

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

#### **Professor Kathryn Abel**

Institute of Brain and Behaviour Mental Health, University of Manchester

#### **Dr David Black**

Medical Director, NHS South Yorkshire and Bassetlaw

#### **David Chandler**

Lay Member

**Gail Coster**

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

**Professor Peter Crome**

Honorary Professor, Dept of Primary Care and Population Health, University  
College London

**Professor Rachel A Elliott**

Lord Trent Professor of Medicines and Health, University of Nottingham

**Dr Nigel Langford**

Consultant in Clinical Pharmacology and Therapeutics and Acute Physician,  
Leicester Royal Infirmary

**Dr Patrick McKiernan**

Consultant Paediatrician, Birmingham Children's Hospital

**Dr Suzanne Martin**

Reader in Health Sciences

**Dr Paul Miller**

Market Access Advisor

**Dr John Radford**

General Practitioner, NHS Sheffield

**Professor Peter Selby**

Consultant Physician, Central Manchester University Hospitals NHS  
Foundation Trust

**Professor Matt Stevenson**

Technical Director, School of Health and Related Research, University of  
Sheffield

**Dr Paul Tappenden**

Reader in Health Economic Modelling, School of Health and Related  
Research, University of Sheffield

**Professor Robert Walton**

Clinical Professor of Primary Medical Care, Barts and The London School of  
Medicine & Dentistry

**Dr Judith Wardle**  
Lay Member

### ***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Pilar Pinilla-Dominguez**  
Technical Lead(s)

**Dr Sally Doss**  
Technical Adviser

**Lori Farrar**  
Project Manager

## **8 Sources of evidence considered by the Committee**

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool reviews and implementation group:

- Fleeman N, Bagust A, Beale S, Boland A, Dwan K, Kotas E, McEntee J, Ahmad S. Ciclosporin for treating dry eye disease: A Single Technology Appraisal. LRiG, University of Liverpool, 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written

submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Santen GmbH

II. Professional/expert and patient/carer groups:

- Royal National Institute of Blind People (RNIB)
- Royal College of Nursing
- Royal College of Ophthalmologists
- Royal College of Physicians
- Royal Pharmaceutical Society

III. Other consultees:

- Department of Health
- NHS England
- NHS Ipswich and East Suffolk CCG
- NHS Shropshire CCG
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Allergan
- Moorfields Pharmaceuticals
- Liverpool Reviews and Implementation Group (LRiG)
- National Institute for Health Research Health Technology Assessment Programme

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on Ciclosporin for treating dry eye disease by attending

the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Francisco Figueiredo, Honorary Clinical professor nominated by Santen – clinical expert
- Dr Kostas Boboridis, Assistant Professor in Ophthalmology, nominated by Allergan – clinical expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Santen