

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Ciclosporin for treating dry eye disease
that has not improved despite treatment
with artificial tears**

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 Ciclosporin is recommended as an option, within its marketing authorisation, for treating severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes.

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. The company presented results from both SANSIKA and SICCANOVE but considered SANSIKA to be most relevant to the decision problem, because it included only people with severe dry eye disease (whereas SICCANOVE included people with moderate to severe dry eye disease). Only details and results of SANSIKA are presented here.
- 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 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.

- 3.4 The efficacy end points were analysed based on the full analysis set (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 analyses for the safety end points were based on the safety analysis set (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. The company carried out several post hoc subgroup analyses including of the primary efficacy end point CFS-ODSI response rate (setting CFS improvement at 3 grades instead of 2).
- 3.5 The company presented the results from SANSIKA for the primary end point and noted that none of the results presented 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.
- 3.6 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 ($p = 0.037$).
- 3.7 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).

- 3.8 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.
- 3.9 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).
- 3.10 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%.
- 3.11 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).

3.12 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).

3.13 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

3.14 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 artificial tears. 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.

- 3.15 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.
- 3.16 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).

- 3.17 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.
- 3.18 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.
- 3.19 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.

- 3.20 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.

3.21 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

3.22 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.

3.23 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 on its own 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.

- 3.24 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.
- 3.25 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.
- 3.26 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.

- 3.27 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 SANSIKA.
- 3.28 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.

- 3.29 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.
- 3.30 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.

- 3.31 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.
- 3.32 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.
- 3.33 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).

3.34 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.

3.35 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).

Company's response to the Committee's request

3.36 The company, in response to consultation, provided a response to all the Committee's requests described in the appraisal consultation document. It did an updated systematic review with the aim of conducting an indirect treatment comparison of the clinical effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, and that of corticosteroids (if needed) plus artificial tears. However, the company stated that a robust indirect comparison was not possible because of methodological problems and the evidence available.

3.37 The company also presented a revised economic analysis of the cost effectiveness of ciclosporin plus corticosteroids (if needed) and artificial tears, and corticosteroids (if needed) plus artificial tears addressing the Committee's request. This cost-effectiveness analysis included:

- the original SANSIKA 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)
- 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.
- 3.38 The company did regression analysis to determine which CFS-OSDI definition of response (the original or the post-hoc definition of response) was a stronger predictor of change from baseline utility at 6 months and found that the effect on utility was greater with the post-hoc definition of response. The company therefore concluded that it was more appropriate to use the post-hoc definition of response in the economic analysis.
- 3.39 The company also did a regression analysis to determine the impact of Sjögren’s Syndrome on utility and concluded that it did not affect health-related quality of life. The company also did a regression analysis to determine whether Sjögren’s syndrome had an impact on response. The results showed that Sjögren’s syndrome was a statistically significant predictor of response at baseline and at 6 months using the original CFS-OSDI response definition and at 3 months using the post-hoc CFS-OSDI response definition.
- 3.40 The company noted that because of the lack of clinical evidence for the comparison of ciclosporin plus corticosteroids (if needed) and artificial tears, with corticosteroids (if needed) and artificial tears, corticosteroids were included in the revised model as a cost parameter only. Based on clinical opinion, the company assumed the composition of corticosteroids to be flouromethalone and prednisolone and duration of treatment with corticosteroids to be 8 weeks. The company also assumed that people whose disease responded to treatment were less likely to need corticosteroids (10% of patients whose disease responded to treatment and 30% of patients whose disease did not respond to treatment).

- 3.41 The company's revised cost-effectiveness analysis when using the post-hoc CFS-OSDI response definition and applying a stopping rule based on the assessment of CFS-OSDI response at 6 months as per its original analysis produced an ICER for ciclosporin plus corticosteroids (if needed) and artificial tears compared with vehicle plus corticosteroids (if needed) and artificial tears of £14,517 per QALY gained, with an associated incremental cost of £709 and 0.05 additional QALYs. When using the trial CFS-OSDI response definition the ICER was £45,554 per QALY gained, with an associated incremental cost of £1161 and 0.03 additional QALYs.
- 3.42 The company also presented a revised cost-effectiveness analysis applying a stopping rule based on the assessment of CFS-OSDI response at 3 months instead of at 6 months as per its original analysis. The ICER for ciclosporin plus corticosteroids (if needed) and artificial tears compared with vehicle plus corticosteroids (if needed) and artificial tears when this assumption was applied was £33,432 per QALY gained, with an associated incremental cost of £425 and 0.01 additional QALYs. When using the trial CFS-OSDI response definition the ICER was £24,696 per QALY gained, with an associated incremental cost of £627 and 0.03 additional QALYs.
- 3.43 The company noted that a gain in utility was seen for people whose disease responded to treatment, regardless of the treatment regimen or response definition. Treatment did not show a significant effect on utility ($p=0.935$), and the company considered that the observed differences in utility between the ciclosporin and vehicle groups were circumstantial. Therefore, the company concluded that it was more appropriate to use pooled utility values in the model.
- 3.44 The company presented a subgroup analysis for people with Sjögren's syndrome which resulted in an ICER for ciclosporin plus

corticosteroids (if needed) and artificial tears compared with vehicle plus corticosteroids (if needed) and artificial tears of £16,231 per QALY gained when using the post-hoc CFS-OSDI response definition, and of £44,874 per QALY gained when using the original trial definition of response.

- 3.45 The company also presented a cost-minimisation analysis comparing different formulations of ciclosporin, assuming that each had equivalent efficacy, adverse event profiles and secondary costs. It noted that the 2% ciclosporin drops formulation developed by Moorfields Pharmaceuticals is no longer available and so the company did not include it in the analysis. The results showed that ciclosporin (Ikervis) is less costly (£72.00 monthly) than Restasis (£454.20 monthly) and Optimune 0.2% ointment (£227.10 monthly).

ERG comments on company's response to the Committee's request

- 3.46 The ERG agreed with the company that it was not possible to do a robust indirect treatment comparison and confirmed that all the requested amendments had been applied in the company's revised cost-effectiveness analysis. However, the ERG considered that the company's revised method for assuming that ciclosporin is dispensed and costed monthly was not accurate. It instead applied its preferred method, incorporating 2 modifications that relate to drug costs during and after the clinical trial.
- 3.47 The ERG noted that the company provided results of regression analyses which supported the use of pooled utility values instead of treatment-specific utility values. The ERG noted that the utility gained from a confirmed response to treatment was substantially greater with vehicle (gain at 6 months=0.095) than with ciclosporin

(gain at 6 months=0.056) and considered that pooling the utility values from both treatment groups introduced bias into the cost-effectiveness analysis, underestimating the utility gain in the vehicle group and overestimating the utility gain in the ciclosporin group. The ERG noted that assuming treatment-specific utility values had a substantial impact on the cost-effectiveness results.

3.48 The ERG presented a preferred scenario analysis that included:

- the original trial definition of response
- the ERG's preferred method to incorporate treatment costs during the trial period
- the ERG's preferred method to incorporate monthly treatment costs
- treatment-specific utility values.

The results from the ERG's preferred scenario showed that ciclosporin plus corticosteroids (if needed) and artificial tears was dominated by (that is, was more costly and less effective than) vehicle plus corticosteroids (if needed) and artificial tears. Ciclosporin plus corticosteroids (if needed) and artificial tears was associated with an associated incremental cost of £1112 and 0.035 fewer QALYs than vehicle plus corticosteroids (if needed) and artificial tears.

3.49 The ERG noted that the company's cost-minimisation analysis results were different from the ERG's results of the analysis presented in the original ERG report (see section 3.37). In particular, the ERG noted that the company concluded that ciclosporin (Ikervis) was over £150 less costly than Optimune and £382 less costly than Restasis per month. The ERG was unable to validate the source of these data, but suggested that the discrepancy may be because the company assumed that patients

have 1 vial of Restasis or 1 tube of Optimune every week, rather than 1 vial or tube per month.

3.50 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. It concluded that corticosteroids (if needed) and artificial tears represent 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 3 different ciclosporin formulations are 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 do 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 Committee noted comments from the company stating that 2% CsA eye drops developed by Moorfields Pharmaceuticals are no longer available in the NHS. However, it heard from the ERG that another 2% CsA eye drop formulation could be sourced. The Committee heard from the company that because this

formulation does not have a marketing authorisation in the UK, it requires additional monitoring incurring additional costs compared with ciclosporin (Ikervis). The clinical experts also noted that Optimune ointment is more widely used in the NHS for people with severe dry eye disease but that some people hesitate to have treatment because of its veterinary marketing authorisation. The clinical experts also noted that it is used at night because it can cause 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 concluded that it was reasonable to assume that the different ciclosporin formulations would show similar efficacy to each other.

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 acknowledged that the vehicle is part of the ciclosporin formulation. The Committee considered that its use as a comparator in the trials limited the interpretation of the results and 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 acknowledged that in response to the Committee's request the company presented the results from an updated systematic review and that the company and the ERG concluded it was not possible to do a robust indirect treatment comparison. The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice that is, corticosteroids (if needed) and artificial tears.

- 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.

- 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 some people with severe dry eye disease might be 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 and thus, in improving quality of life. The Committee had reservations about all the post hoc analyses presented by the company and considered that these analyses were not sufficiently robust. It concluded that the original CFS-OSDI response data was more appropriate to assess 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 showed 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 original model was only 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 had provided the amendments it requested in the appraisal consultation document (see section 3.37), by presenting an updated economic model that compared ciclosporin plus corticosteroids (if needed) and artificial tears with vehicle plus corticosteroids (if needed) and artificial tears. The Committee discussed that this updated model included

corticosteroids as a cost parameter only, and so any potential advantage of lower stopping rates in the ciclosporin group because of corticosteroids (see section 4.1) was not explored. Moreover, results from the vehicle group in SANSIKA were still used as a proxy for the comparator group in the model. The Committee concluded that both models provided by the company were only of limited relevance for its decision-making.

- 4.11 The Committee nevertheless explored the results from both the company's original and updated models. It noted that there were 3 main drivers of the results and discussed them in turn. It noted that the company used the post-hoc analysis for CFS-OSDI response in its base-case analysis in its original and updated models, 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, from £14,500 to £45,600 per quality-adjusted life year (QALY) gained (see section 3.41). However, it also noted that this did not occur if a 3-month (as opposed to 6-month) stopping rule for ciclosporin was applied resulting in an ICER of £33,400 per QALY gained when using the CSF-OSDI post-hoc response definition and £24,700 per QALY gained when using the original CFS-OSDI response definition (see sections 3.42 and 4.12). The Committee noted that these differences were carried through to the results from the updated model. 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).

4.12 The Committee considered the ERG's concerns about how stopping treatment had been modelled in the company's original base-case analysis. The Committee noted that in the original model, 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 rate subsequently remained stable. In contrast, 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 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. The Committee also noted that the company, in its updated model, provided the results of the cost-effectiveness analysis assuming a different stopping

rule at 3 months (based on CFS-OSDI assessment at 3 months instead of 6 months, as per its original analysis) and that the ICER for ciclosporin plus corticosteroids (if needed) and artificial tears compared with vehicle plus corticosteroids (if needed) and artificial tears was lower when this assumption was applied (see section 4.11). The Committee concluded that it was unclear when treatment with ciclosporin would be stopped in clinical practice because corticosteroids' potential effect on stopping rates had not been included in the company's updated model.

- 4.13 The Committee discussed the utility values used in the original 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 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 (that is, it was both more costly and less effective than) vehicle plus artificial tears. The Committee noted that the company still used pooled utility values in its updated model and that the company stated that any differences in utility values

between treatment groups were circumstantial. The Committee also noted comments from a clinical expert stating that adverse effects with ciclosporin are transient and have limited impact on quality of life. The Committee recognised that the cost-effectiveness results varied substantially when applying treatment-specific utility values, but was also aware that the analyses did not capture corticosteroids' potential to mitigate adverse effects (see section 4.2). The Committee concluded that this added additional uncertainty to the results presented by the company.

4.14 The Committee noted that in its original 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). The Committee noted that the company provided a subgroup analysis for people with Sjögren's syndrome in its updated model. However, this subgroup analysis incorporated the same assumptions as the analysis for all patients (see section 4.10) and the Committee concluded that these results also lacked relevance for its decision-making.

4.15 The Committee summarised its considerations about the company's original and updated models. Firstly, it considered that the models lacked relevance because the comparator used was vehicle rather than corticosteroids (if needed) and artificial tears, which is considered established clinical practice (see sections 4.9 and 4.10). The Committee considered that the vehicle's independent characteristics may have affected the results of the model, because vehicle alone showed benefits in terms of CFS-OSDI response rate (see sections 4.4 and 4.5). The Committee

acknowledged that the vehicle may be associated with some benefit but highlighted that it was not commercially available on its own in the UK. Secondly, the Committee noted that 3 parameters had a substantial effect on the cost-effectiveness results (namely, using the original or post-hoc CFS-OSDI response definition, a 3- or 6-month stopping rule, and pooled or different utility values for treatment groups) and that changing them led to very variable results (see sections 4.11–4.13). The Committee considered it was difficult to draw any conclusions from a model subject to these assumptions and with a non-relevant comparator.

- 4.16 The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available. It therefore discussed the ERG's and the company's cost-minimisation analyses comparing ciclosporin (Ikervis) with the other ciclosporin formulations. It noted that based on the ERG's analysis, ciclosporin (Ikervis) was less costly than Restasis and that there was not a big cost difference compared with the other ciclosporin formulations. It also noted that based on the company's analysis, ciclosporin was the least expensive and that the differences between the company's and the ERG's estimates were based on different assumptions in the number of vials and tubes of ciclosporin needed per month. The Committee understood that other ciclosporin formulations that do not have a marketing authorisation in the UK require additional monitoring, whereas this is not needed with ciclosporin (Ikervis; see section 4.2). The Committee noted comments from a clinical expert and the company that if ciclosporin (Ikervis) were not recommended for use in the NHS, other ciclosporin formulations that do not have marketing authorisation in the UK (and are associated with higher costs) would continue to be used. The Committee restated its previous conclusion that it was reasonable to assume that the different

ciclosporin formulations would show similar efficacy (see section 4.1) and considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that, on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears.

- 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 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.

4.18 The Committee was aware of the NICE’s [position statement](#) about the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism. It acknowledged ‘that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal of ciclosporin. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the cost effectiveness of ciclosporin.

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
Key conclusion		
Ciclosporin is recommended as an option, within its marketing authorisation, for treating severe keratitis in adult patients with dry eye disease that has not improved despite treatment with tear substitutes.		1.1
The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available. It considered that it was reasonable to assume that the different ciclosporin formulations would show similar efficacy to each other. The Committee also considered that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations. Therefore, the Committee concluded that,		4.2, 4.16

<p>on balance, ciclosporin (Ikervis) was a cost-effective use of NHS resources for people with severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with artificial tears.</p>		
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee noted 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>	4.17
	<p>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.</p>	4.1
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related</p>	<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</p>	4.17

benefits?	<p>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>	
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 marketing authorisation.	4.1
Adverse reactions	<p>The most common adverse reactions with ciclosporin are eye pain, eye irritation, lacrimation, ocular hyperaemia and eyelid erythema.</p> <p>The Committee noted comments from a clinical expert stating that adverse effects with ciclosporin are transient and have limited impact on quality of life.</p>	<p>2.3</p> <p>4.13</p>
Evidence for clinical effectiveness		
Availability, nature and quality of	The Committee discussed the clinical effectiveness evidence for ciclosporin. It	4.3

evidence	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.	
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 that is, corticosteroids (if needed) plus artificial tears.	4.4
Uncertainties generated by the evidence	<p>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.</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 that is, corticosteroids (if needed) plus artificial tears.</p> <p>The Committee had reservations about the</p>	<p>4.5</p> <p>4.4</p>

	post hoc analyses presented by the company and considered that these analyses were not sufficiently robust.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee concluded that ciclosporin plus artificial tears showed greater benefits compared with the vehicle plus artificial tears in the subgroup of people with Sjögren's syndrome and severe dry eye disease.	4.8
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that it had not been presented with evidence on the relative clinical effectiveness of ciclosporin compared with established clinical practice that is, corticosteroids (if needed) plus artificial tears.	4.4
	The Committee noted that, based on the evidence presented, ciclosporin had not shown superior clinical effectiveness to the vehicle.	4.5
	The Committee considered other commercially available ciclosporin formulations and concluded that it was reasonable to assume that the different ciclosporin formulations would show similar efficacy to each other.	4.2
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the cost-effectiveness evidence presented by the	4.9

	<p>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.</p> <p>The Committee noted that the company had provided the amendments it requested in the appraisal consultation document by presenting an updated economic model that compared ciclosporin plus corticosteroids (if needed) and artificial tears with vehicle plus corticosteroids (if needed) and artificial tears.</p>	<p align="center">4.10</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that the company's updated model included corticosteroids as a cost parameter only and that results from the vehicle group in SANSIKA were still used as a proxy for the comparator group in the model. The Committee concluded that the company's original and updated model were only of limited relevance because they failed to show the cost effectiveness of ciclosporin compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears.</p> <p>The Committee restated its concerns about</p>	<p align="center">4.9, 4.10</p>

	<p>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.</p> <p>The Committee concluded that it was unclear when treatment with ciclosporin would be stopped in clinical practice because corticosteroids’ potential effect on stopping rates had not been included in the company’s updated model.</p> <p>The Committee recognised that the cost-effectiveness results varied substantially when applying treatment-specific utility values but was also aware that the analyses did not capture corticosteroids’ potential to mitigate adverse effects. The Committee concluded that this added additional uncertainty to the results presented by the company.</p>	<p>4.11</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 significant and substantial health-related benefits been identified that were not included in</p>	<p>The Committee noted that the company used pooled EuroQoL 5D questionnaire (EQ-5D) data from SANSIKA for both response and non-response.</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</p>	<p>4.13</p> <p>4.17</p>

<p>the economic model, and how have they been considered?</p>	<p>captured in the QALY calculation.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee noted that the company provided a subgroup analysis for people with Sjögren’s syndrome in its updated model. However, this subgroup analysis incorporated the same assumptions as the analysis for all patients and the Committee concluded that these results also lacked relevance for its decision-making.</p>	<p>4.14</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee noted that 3 parameters had a substantial effect on the cost-effectiveness results (namely, using the original or post-hoc CFS-OSDI response definition, a 3- or 6-month stopping rule, and pooled or different utility values for treatment groups) and that changing them led to very variable results.</p>	<p>4.15</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee concluded that the company’s original and updated model were only of limited relevance because they failed to show the cost effectiveness of ciclosporin compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears.</p> <p>The Committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available.</p> <p>The Committee considered that the different</p>	<p>4.9, 4.10 4.16</p>

	ciclosporin formulations would show similar efficacy and concluded that, based on the cost-minimisation analyses presented by the company and the ERG, the cost of ciclosporin (Ikervis) was reasonable compared with the other ciclosporin formulations.	
Additional factors taken into account		
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 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has dry eye disease which has not improved despite treatment with artificial tears and the doctor responsible for their care thinks that ciclosporin is the right treatment, it should be available for use, in line with NICE’s recommendations.
- 5.4 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [[NICE to amend list as needed at time of publication](#)]
- Slides highlighting key messages for local discussion.
 - Costing template and report to estimate the national and local savings and costs associated with implementation.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 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).

7 Review of guidance

7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
October 2015

8 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 Iain Miller

Founder and CEO, Health Strategies Group

Dr Paul Miller

Market Access Advisor

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School/Senior Clinical University

Teacher, University of Glasgow

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 and Raisa Sidhu

Technical Advisers

Lori Farrar

Project Manager

9 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 Pharmaceutical 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 Pharmaceutical