NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA369; Ciclosporin for treating dry eye disease which has not improved after treatment with artificial tears

Original publication date:	December 2015
Review date	December 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA369, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

No new evidence has been identified that is likely to change the recommendations in TA369.

The company has confirmed that no changes are anticipated in marketing authorisation of ciclosporin (Ikervis).

3. Summary of new evidence and implications for review

Original guidance:

Two trials, SANSIKA and SICCANOVE were identified. These trials compared ciclosporin (Ikervis, a 0.1% ophthalmic emulsion formulation of ciclosporin) with a vehicle in people with dry eye disease that had not improved despite treatment with artificial tears. However, SANSIKA was the key trial in the submission because it included only people with severe dry eye disease, in line with the marketing authorisation (whereas SICCANOVE included people with moderate to severe dry eye disease).

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.

The committee considered other commercially available ciclosporin formulations (0.2% and 2% formulations). It agreed that it would have liked to have seen a scenario analysis comparing 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. It therefore 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.

New evidence:

A number of publications based on SANSIKA and SICCANOVE were identified.[1-8] However, no new evidence comparing Ikervis (0.1% ophthalmic emulsion formulation of ciclosporin) with another treatment was found. Similarly, no new registered and unpublished trials with Ikervis were identified.

A number of studies with other cyclosporine solutions of various strengths were identified:

One study compared steroidal eye drops (0.1% fluorometholone; plus 0.1% sodium hyaluronate) with 0.5% ciclosporin solution (brand name unknown; plus 0.1% sodium hyaluronate) in patients with Sjögren's syndrome in Hospital of Fudan University, in Shanghai, China; after 8-weeks treatment, similar improvements were found for both treatments.[9] The same study was also the only included study assessing cyclosporine in a systematic review of randomized controlled trials in the treatment of dry eye disease in Sjögren's syndrome.[10] In addition, one registered and unpublished trial is comparing Restasis (0.05% ophthalmic emulsion formulation of ciclosporin) with corticosteroids (Lotemax, see section 3 Appendix C).

Two studies comparing Restasis and other ciclosporin formulations, were identified; Clacier[11] (0.05% solution) and Cyporin N[12] (0.05% solution). In addition, four registered and unpublished trials are comparing Restasis with another ciclosporin solution, but none of these included Ikervis (see section 3 in Appendix C).

Five studies compared ciclosporin with lubricant or vehicle. However, none of these used Ikervis.[13-17] Seven registered and unpublished trials are comparing ciclosporin with lubricant or vehicle, but none of these included Ikervis (see section 3 in Appendix C).

One systematic review of 0.05% cyclosporine was identified, but the literature searches were performed in July 2013 and only studies comparing cyclosporine with artificial tears, placebo (vehicle) and without topical treatment were included. The results were pooled across the comparators and showed improvements but also noted more adverse effects with cyclosporine.[18]

However, the new evidence is unlikely to change the recommendation in TA369.

Implications for review:

In the original guidance, a cost-minimisation analyses was the basis for the committee's decision and the cost of Ikervis was compared with other ciclosporin formulations.

No other cyclosporine formulations currently have a marketing authorisation for treating dry eye disease. Ikervis is the only licensed and recommended ciclosporin treatment for this condition.

The cost of Ikervis has not changed since the original guidance was published.

No new evidence has been identified that is likely to change the recommendations in TA369.

Has there been any change to the price of the technology(ies) since the guidance was published?

No, there have been no changes to the pricing of ciclosporin (Ikervis) since the guidance was published.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

In the original guidance TA369, the committee identified several issues (see below). However, no relevant new evidence regarding these issues was identified.

Clinical effectiveness:

- SANSIKA, the key trial: 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 measure of corneal damage (CFS) over time and in measure of inflammation (human leukocyte antigen-DR; HLA-DR). The committee noted that, based on the evidence presented, ciclosporin had not shown superior clinical effectiveness to the vehicle.
- Company's meta-analysis: 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.
- 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.

***Cost-effectiveness*:**

- The company's model used the results from the vehicle group in SANSIKA as a proxy for corticosteroids (if needed) and artificial tears.
- 3 parameters had a substantial effect on the cost-effectiveness results: 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.

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 plus corticosteroids (if needed) and artificial tears compared with established clinical practice in the NHS, that is corticosteroids (if needed) plus artificial tears.

Cost-minimisation analyses:

- The committee agreed that it was relevant to consider ciclosporin (Ikervis) in comparison with other ciclosporin formulations available.
- The committee considered that the different ciclosporin formulations would show similar efficacy

The committee 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.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None.

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from 22nd December 2014 to 1st October 2018 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues were raised during the original guidance development.

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of ciclosporin within its marketing authorisation for treating dry eye disease

6. Current guidance

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

7. Research recommendations from original guidance

Not applicable

8. Cost information from original guidance

£72 (excluding VAT) for a monthly course

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

LipiFlow thermal pulsation treatment for dry eyes caused by blocked meibomian glands (2015) NICE Medtech innovation briefing MIB29

In progress

Lifitegrast for treating dry eye disease. NICE technology appraisal. Publication date to be confirmed.

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes. The cost of ciclosporin eye drops was £72 per month, excluding VAT.	No change.

3. Registered and unpublished trials

Trial name and registration number	Details
Trials comparing ciclosporin formulations	
Efficacy and Safety Study of Haporine-S in Subjects With Moderate to Severe Dry Eye, A Multicenter, Investigator(Assessor) Blind, Parallel Design, Non-inferiority Phase III Trial NCT01804361; UMT-2012-DH-HS-01; 1360-8040-3073-4190	RCT of 0.05% ciclosporin (Restasis) vs. Haporine-S, a nanoparticle-based ciclosporin formulation n = 90 Completed ~February 2014

Appendix C

Trial name and registration number	Details
Efficacy and Safety of HU007 Eye Drops in Patients With Dry Eye Syndrome NCT03461575; HU-007_P3	RCT of 0.05% ciclosporin (Restasis) vs. 0.02% ciclosporin with 3% trehalose (HU007) vs. 3% trehalose (Moisview) n = 213 Estimated completion date: July 2018 Recruitment status given as “currently enrolling by invitation”
Efficacy and Safety of HE10 for Dry Eye Syndrome NCT02492412	RCT of 0.05% ciclosporin (Restasis) vs. HE10, a nanoparticle-based ciclosporin formulation n = 101 Completed, September 2014
A Multicenter, Randomized, Double-blind Phase III Study of Cyclosporine Ophthalmic Soution Group and Cyclosporine Ophthalmic Suspension Group 12 Weeks After Treatment in Moderate to Severe Dry Eye Disease NCT01768312; HL_TSPR_301	RCT of 0.05% ciclosporin solution (Restasis) vs. 0.05% ciclosporin suspension (Tisporin) n = 84 Completed ~July 2013
Trials comparing ciclosporin and corticosteroids	
Treatment of Ocular Graft-versus-Host Disease (GVHD) With Topical Loteprednol Etabonate 0.5% NCT01695668; Lotemax_00045815; Lotemax_BMT	RCT of topical corticosteroid (Lotemax) vs. 0.05% ciclosporin solution (Restasis) n = 75 Completed: February 2015
Trials comparing ciclosporin with other solutions	
Phase 3 Study of OTX-101 in the Treatment of Keratoconjunctivitis Sicca NCT02688556; OTX-101-2016-001	Randomised controlled trial (RCT) of 0.09% ciclosporin ophthalmic solution (OTX-101) vs. placebo (vehicle without ciclosporin) with subsequent open-label extension n = 745 Completed ~ December 2016

Trial name and registration number	Details
An Open-Label Extension of a Phase 3 Study of OTX-101 in the Treatment of Keratoconjunctivitis Sicca NCT02845674; OTX-101-2016-002	Single group extension to the above study. n = 145 Completed ~August 2017
The Comparison of 50 % Concentration Autologous Serum Eye Drops Versus Preservative Free Artificial Eye Drop Plus 0.05 % Ciclosporin Ophthalmic Emulsion in the Treatment of Severe Dry Eye Syndrome: A Randomized Comparative Study NCT03666884; UsakSH	RCT of 0.05% ciclosporin (Restasis) vs. autologous serum eyedrops n = 36 Completed ~October 2016
The Effects of Cyclosporin A Emulsion, (Restasis), on the Ocular Surface in Response to Low Humidity Environment in Patients With Dry Eye NCT02199964; H-33276	RCT of 0.05% ciclosporin (Restasis) vs. artificial tears n = 20 Completed ~December 2015
A Phase 2b/3, Multicenter, Randomized, Double-masked, Vehicle-controlled Clinical Study to Assess the Efficacy and Safety of Topical CyclASol® for the Treatment of Signs and Symptoms of Dry Eye Disease NCT03292809; ESSENCE; CYS-003	CyclASol is a ciclosporin solution. In the prior phase II trials 0.1% and 0.05% solutions were used. The strength of the solution used in the present trial isn't clear n = 328 Active, not recruiting Estimated completion date: July 2018 (primary outcome); December 2018 (overall)
Efficacy and safety assessment of t1580 versus vehicle in dry eye disease treatment 2015-005405-36; LT1580-301	RCT of 0.1% ciclosporin solution (t1580) vs. vehicle n = 450 Ongoing 3 year trial, start date not given.

4. Implementation

Not applicable

Appendix D – References

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