NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ciclosporin for treating dry eye disease [ID665]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Francisco C Figueiredo, MD, PhD, FRCOphth

Name of your organisation: Royal Victoria Infirmary, Department of Ophthalmology, Newcastle upon Tyne NHS Hospitals Foundation Trust.

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? √
  - Prof. Figueiredo, MD, PhD, FRCOphth is a Consultant Ophthalmologist in the Department of Ophthalmology at the Royal Victoria Infirmary (Newcastle upon Tyne, UK) and Professor of Ophthalmology at Newcastle University.
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
For people with dry eye disease (DED), preservative-free artificial tears are currently used as first line suitable therapy. Ocular lubricant ointment should be used at night as ointments containing paraffin/lanolin and may cause discomfort and blurred vision. Cyclosporin (CsA) is mostly used for severe VKC, AKC and other autoimmune syndromes such as severe DED in Sjogren's patients (ointment only in the UK). However, for DED patients, more importantly in moderate (not responding to traditional treatment) and severe cases, CsA products must be considered, however in some centres in the UK CsA may be considered a second line treatment. Short courses of corticosteroids (i.e. pulse therapy) are often used but should be used under ophthalmological supervision due to potential serious sides effects (e.g. cataract, ocular hypertension).

Is there significant geographical variation in current practice? Unfortunately, it is not currently known. As far as I know there is no known data available.

Are there differences of opinion between professionals as to what current practice should be? Not that I am aware of.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? There is no active valid comparator in the absence of an approved product in the EU countries. However, I believe unlicensed preparations of CsA are listed on most UK formularies.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Patients with more severe forms of DED are more often associated with systemic autoimmune diseases such as Sjogren's syndrome and GVHD.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? CsA formulation can potentially benefit all forms of DED, more importantly it should not put at risk any patient with any form of DED.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Patients seeking medical service for DED are asked to visit their GP for consultation first. GPs will refer DED patients to an optometrist or an ophthalmologist for diagnosis, if symptoms persist despite initial treatment, or are moderate/severe. The majority of care provided to moderate/severe DED cases are managed by ophthalmologists in a tertiary setting. Patients are unstructured to periodically collect repeat prescription from their referring GP. Therefore, as CsA therapy provides an additional option to other active treatments without the need for incremental specialist or technologically advanced monitoring or care, its availability will not alter the current clinical pathway of care.

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Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Not that I am aware of.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Ophthalmologists in the UK, in both public and private sector, currently prescribe unlicensed CsA. CsA hospital-compounded formulations are diverse with 0.05% to 2% ophthalmic solution (in olive or castor oil) or ointment administered up to four times daily (Table 1).

Table 1: Prescription of CsA in the UK

Indications ranking	Treatment line	Concentration of CsA	Posology
AKC&VKC (+++)	First/second line	0.06%; 0.2%;2%	2-4 drops/day
Dry eye disease (Sjögren's syndrome) (++)	Second line		
Prevention of corneal graft rejection (+)	First/second line	2%	4-6 drops/day

The indication to prevention of corneal graft rejection is acceptable but I am not aware of many surgeons using this protocol routinely in the UK.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
Clinical guidelines recommend using CsA when tear substitutes are inadequate (DEWS, 2007) and for moderate to severe DED (American Academy of Ophthalmology 2013). I am not aware of a specific guideline within the UK.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
Appropriate patient selection for the technology should be guided by treatment failure with adequate initial use of artificial tear substitutes and by severity of keratitis (i.e. punctate epithelial erosion) at presentation in DED. As patients, who may be eligible for the new technology, are already in the DED treatment pathway, the determination of DED severity with additional tests/investigations after failure with initial appropriate use of tear substitutes is likely to be performed with or without the technology before

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a decision is made regarding additional treatment options. The frequency of topical CsA administration (by the patients themselves) is likely to be lower compared with that of standard artificial eye drops, and administration of the technology by a healthcare professional is not required. Due to a negligible systemic absorption of topical CsA there is no requirement for monitoring patients over and above usual clinical practice. A reduction in the use of concomitant Artificial Tears (ATs)may be observed with the use of topical IKERVIS. In addition, the number of topical steroid pulse therapy per year may also be reduced over time with the topical use of IKERVIS.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
The Summary of the Product Characteristics (SmPC) does not identify any stopping rule. However the presence of keratitis should be reassessed every visit by the ophthalmologist.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.
The use of the technology under clinical trial conditions is expected to reflect what it is observed in clinical practice since IKERVIS used during the clinical trials exactly mimicked current clinical practice as it was used concomitantly with ATs.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?
Yes since during clinical trials IKERVIS was used concomitantly with ATs. Please also see my answer to the above question.

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
The most important outcome was the reduction of keratitis and inflammation. Patient's symptoms did improve from baseline even if not statistically significantly different from the Vehicle. More importantly, in addition to the improvement of patient reported symptoms, the ocular surface damage improvement is regarded as more relevant as patients presenting with keratitis are at greatest risk of serious complications such as secondary infection and permanent damage with corneal scar formation and potentially visual loss.

What is the relative significance of any side effects or adverse reactions?
Overall the safety profile of the technology in patients with severe DED is characterised by local ocular adverse reactions at instillation site (≤1/10, in accordance with the EMA classification) and common adverse reactions (≤1/100 to <1/10) including eye disorders only (e.g. conjunctival hyperemia, erythema of eyelid, eye irritation, eye pain, itchy eye, eyelid edema, watery eye, ocular hyperemia, photophobia, among others). Non-severe adverse reactions were managed by either temporary or permanent cessation of treatment and severe adverse reactions by

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permanent cessation of treatment. No further treatment was utilised in the management of adverse reactions.

In what ways do these affect the management of the condition and the patient's quality of life?
Improvement in EQ-5D as secondary endpoint improved in both groups (IKERVIS and vehicle control) over time, but not significantly. However, objective signs correlate poorly with symptoms, the incremental health-related benefits of CsA, relative to vehicle, are driven by objective outcomes associated with eye health including corneal staining, ocular surface inflammation and tear osmolarity.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
N/A as IKERVIS is not yet on the market. However, it is not the case with current unlicensed CsA products.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I am not aware of any potential issues related to equality and diversity.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence?
Not that I am aware of.

This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.
N/A

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

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Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?
As unlicensed topical CsA is already widely used in the UK the technology will facilitate/maximise prescription by local GPs under guidance by the ophthalmologist and avoid the inconvenience to patients of frequent returns to the hospital for repeat prescription and potentially improve compliance with treatment.

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
As the technology is administered topically, there are no extra education and training resource needed for the NHS, other than the cost of technology itself.