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: Kostas G Boboridis

Name of your organisation
Oculoplastic Fellow in Moorfields Eye Hospital
Assistant Professor in Ophthalmology, Aristotle University, Thessaloniki, Greece

Are you (tick all that apply):

- **X** 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.)?
- 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?
Dry eye is currently treated by basic artificial tear drops, gels and ointments with or without topical steroids when required. Premium artificial tears or targeted treatment methods are rarely used in non specialist clinics.

Is there significant geographical variation in current practice?
Geographical variation depends on the presence of specialist centres or not and the economic limitations on prescription items.

Are there differences of opinion between professionals as to what current practice should be?
Some documented differences of opinion may exist between experts in the field with no significant deviations from a uniform management strategy. Primary care and GP practices may have different more simplistic approaches mainly due lack of evidence and financial restrictions.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
The need for local anti-inflammatory and immunomodulatory treatment in dry eye is partly met with the use of topical steroids. The rapid onset of action is counterbalanced by limitations of indication for short term use, potential intraocular pressure elevation, early cataract formation and risk of infections.
A non branded alternative of the same active ingredient is the topical Ciclosporin preparations made by local pharmacies, lacking consistency in concentration and vehicle, usually with reduced tolerability.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Those with predominant inflammatory – autoimmune causes of dry eyes like Sjogren syndrome or autoimmune disorders where topical Ciclosporin is highly indicated. Similarly, the advanced stages of the disease (DEWS stage3, 4) regardless of the causative factor depend on inflammatory control to halt progression to potentially blinding corneal and ocular surface disease.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
Current practice and evidence from the long term use of one extensively used commercial preparation of Ciclosporin suggests that the benefit is proportional to the severity of the disease and stretching it to the extreme is even recommended as first line treatment in the USA. As studies may confirm there are no serious side effects related to the use of the drug with topical irritation and tolerability issues being the most prominent.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

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Initially, the use may be restricted to specialist clinics only as an advanced treatment for a very common condition. Recommendations for practice along with clinical data will derive from those centres and potentially allow for broader use by physicians in all levels of patient care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
As described above, this should only be allowed at a later stage when evidence and practice would have matured on a specialist level and certainly with some form of control and indications due to cost implications

If the technology is already available, is there variation in how it is being used in the NHS?
The technology is indirectly available as non branded pharmacy preparations which are lacking the beneficial effect of the vehicle of the branded commercial preparations. Still, it is not uniformly used as some areas have easier access and better expertise.

Is it always used within its licensed indications? If not, under what circumstances does this occur?
The branded preparations are licenced for the treatment of dry eyes. This is the leading indication for the use of topical Ciclosporin. As a potent anti-inflammatory and immunomodulatory drug it is being used of-licence for vernal and atopic keratoconjunctivitis, Meibomian gland dysfunction and for a number of inflammatory ocular surface conditions or cicatrising conjunctivitis. In addition, it is used to prevent corneal graft rejection and where steroids are required but contraindicated.

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.
Unfortunately, the fact that only one commercially available preparation is licenced for the treatment of dry eyes is limiting our knowledge and restricts the guidelines to those developed for this specific preparation. All these are based on the available USA data and experience, posing a strong need for a fresh objective view from Europe and specifically the UK. It is therefore not justified to have a strong view about any aspect of it but to collect the evidence and base the clinical guidelines on available data.

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?

Since there are not commercially available alternatives, the technology will address an unmet need for the adjunctive treatment of a very common disorder. It will be as easy to use as any topical eye drop preparation and ideally it can be another strong

tool in our management options for dry eyes which will certainly supplement concomitant treatment for the condition with no additional requirements.

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.
One recommendation may be for dry eyes stage 3 or 4 and Sjogren syndrome. The additional testing is what clinical practice may require to identify those patients.
Initiation of treatment may be on diagnosis and data from the USA suggests that the effect may take 2-4 months to manifest and that minimum period of treatment is six months. Following this, prolonged is safe when required for controlling the disease of only the exacerbations.
Response to treatment may be assessed by improvement on signs and symptoms (at least one of each) or be detecting reduction in one of several inflammatory markers on the tear film of dry eyes.

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.
Clinical trials, both in the USA and Europe were multicentre with similar clinical settings as those observed in the majority of ophthalmic units or practices that focus on the disease.

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?
We may consider the trial setting very similar to current NHS clinical practice but not the community are or GP practice. One mail difference may be the busy UK timeframe with high targets to meet resulting in limited quality assessment time spend with patients.

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 USA trials were based on reduction of at least one sign and symptom whereas some European trials were based on the reduction of a detectable inflammatory marker. Both address important issues on the disease process but they do not allow to predict long term outcome as in most cases treatment only controls the disease rather than actually providing permanent cure.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
No significant adverse reactions were reported with most confined to topical irritation and poor tolerability. There is strong evidence that dry eye is significantly diminishing quality of life and functionality both for visual and everyday tasks. The beneficial effect of successful treatment is reversing the detrimental effect on quality of life. Since Ciclosporin is considered a key treatment option with favourable outcome, it is understandable to see an improvement on quality of life.

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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;
- 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

There are no obvious issues with equality or discrimination for any possible group of people with protected characteristics of any kind that can relate to this technology. The only potential problem to be solved will be the potentially high cost and the availability on the NHS

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? 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.

As the available commercial preparations are very limited, every information related to the technology is published with long track of trials or case series studies. Clinical practice does not differ significantly from the trials setting. Potential commercial bias may be detected in some of the publications as most refer to one branded preparation with strong financial interest. Nevertheless, having more than one preparations tested in trials will give us more objective and balanced results on efficacy and safety.

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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.

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? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra provision for training and facilities is required for the implementation of this treatment that is as simple as any other eye drop to use, significantly safe and is self-administered by patients.
The possible high cost of the commercial preparations may become an issue for recommending and prescribing the drug for a very frequent disease especially for the age group over 50 years of age.
This can only be seen in conjunction with the estimated cost from decreased functionality, days of sick, hospital and GP visits as well as long term specialist management of severe end stage ocular surface and corneal damage.