Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ciclosporin for treating dry eye disease [ID665]

Thank you for agreeing to make a submission on your organisation's 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 submission, 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: [redacted]), and [redacted])

Name of your organisation: the Royal College of Nursing
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)?

- **(v)** - 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)? [redacted]

- **Other**

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

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

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?

*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.*

As stated in the final scope document, Dry Eye Disease (DED) is categorised based on severity of the condition (Dry Eye Workshop classification system). This classification system is utilised in the NHS setting and thus underpins treatment algorithms, ranging from topical lubricants for DEWS 1 to immunosuppressants and surgery for DEWS 3 – 4. The literature supports the safety and efficacy of ciclosporin as an immunomodulatory topical agent for the treatment of DED. Other immunomodulators, tacrolimus and tofacitinib have been used in pilot studies with promising results ([i], [ii]).

It is recognised that patients react to treatment differently and as such alternatives are required. Case in point, patients who are deemed to be steroid responders may respond to immunomoduators and or anti-inflammatory agents (tetracycline). However, care should be taken in the administration of such treatment to high risk groups in line with the summary of product characteristics. It should be noted, nevertheless, that Ciclosporin is used currently for patients with DED DEWS 3-4 as other treatments have not provided symptomatic or pathological relief to patients.

Dry Eye Disease is treated with artificial tears and lubricants. Ciclospsorin is not the drug of choice and is used at the end stage of dry eye disease. The drug is expensive but is used in the United States of America. Artificial tears are also sometimes used in conjunction with Ciclosporin Eye drops; and the patient could have been treated with Ciclosporin for their underlying condition.

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Currently, the technology is used off-label for DED in the UK. As such, increased care and treatment supervision is required in secondary care (medical professional use only). Some treatment facilities employ specialist nurses to aid the medical team in monitoring the systemic condition of the patients as a result of this technology and other treatments. However, once regulated, this technology can be used in settings with advanced ophthalmic nursing and optometrist practitioners working to a treatment protocol with the support of an ophthalmology consultant.

We feel that if prescribed in the secondary setting, measures should be put in place to monitor the effectiveness and side effects of the treatment and progression of the condition.

It is not clear from the evidence if Ciclosporin is the best treatment; however this could suggest that clear assessment should be made of eligible patients as an individual approach to prescribing is important.

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?

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.

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. 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? 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?

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?

The technology is currently being used off-label for DED in secondary/tertiary ophthalmic care centres in the UK. Alternatives with the same treatment modality are used in other ophthalmic conditions but have undergone pilot trials for use in

DED. Patients on long term systemic Ciclosporin are at risk of infection. Following a favourable NICE recommendation, patients will have increased access to treatment with this technology. In-depth pre-treatment criteria and post treatment monitoring regimes already accompany treatment plans for each patient. However, NICE recommendation will give the patients and the public a greater understanding of the need for such rigorous monitoring regimes thereby increasing patient knowledge and patient choice.

The following is an example of a pre-treatment checklist at an institution that currently uses Ciclosporin for DED:

Contra-indications: Ciclosporin is contra-indicated in patients with a hypersensitivity to Ciclosporin or to any of the ingredients of the formulation. It should also not be used in patients with uncontrolled arterial hypertension, uncontrolled infections (including viral) and malignancies. Be extremely careful in patients with impaired renal function or in elderly patients.

1. ***Complete medical history; ask especially for arterial hypertension, renal dysfunction, active/untreated infections, tuberculosis, chickenpox, malignancies and pregnancy.***

2. ***Complete drug history. Ask also for self-administered medications and dietary supplements!***
   Drugs that may potentiate renal dysfunction:
   Antibiotics: gentamicin, tobramycin, vancomycin, trimethoprim with sulfamethoxazole
   Antineoplastics: melphalan Antifungals: ketoconazole, amphotericin B
   Anti-inflammatory Drugs: azapropazone, diclofenac, naproxen, sulindac, colchicine
   Gastrointestinal Agents: cimetidine, ranitidine
   Immunosuppressives: tacrolimus
   Drugs that increase Ciclosporin concentrations:
   Calcium Channel Blockers: diltiazem, verapamil, nicardipine
   Antibiotics: clarithromycin, erythromycin, doxycycline, quinupristin/daldopristin
   Antifungals: fluconazole, itraconazole, ketoconazole
   Glucocorticoids: methylprednisolone
   Other Drugs: colchicine, amiodarone, allopurinol, danazol, metoclopramide, bromocriptine, HIV protease inhibitors, grapefruit juice
   Drugs/dietary supplements that decrease Ciclosporin concentrations:
   Antibiotics: nafcillin, rifampin
   Anticonvulsants: carbamazepine, Phenobarbital, phenytoin
   Other Drugs: octreotide, ticlopidine, orlistat, St. John's Wort

Other drug interactions: Potassium sparing diuretics, digitoxin, lovastatin

3. ***Check blood pressure, blood sugar levels and weight.***

4. ***Laboratory tests: Full blood count, electrolytes, liver and kidney profile, serum lipids. (At least two individual creatinine levels should be obtained to assess baseline kidney function). If there is a negative history of chickenpox or if there is any doubt, test for Varicella zoster virus antibodies.***

Information for patients: Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. They should be given careful dosage instructions, advised of the potential risks during pregnancy. Patients receiving Ciclosporin should be instructed to report immediately any evidence of infection. Advise patients to avoid self-medication with over-the-counter NSAIDs because of potential nephrotoxicity. Patients should not drink grapefruit juice 1 hour prior to oral dosage.

Overall, the clinical trial conditions, that is, patient population and disease demographic grossly reflects clinical practice. However, due to the heterogeneity of trial methodology and outcomes, it may be difficult to conduct a meta-analysis of the available data. From the patient's perspective, ocular symptom relief is of the utmost importance. Thus, outcome measures evaluating some or all of the known symptoms were noted in the literature. Other outcome measures such as amelioration of tear film break up time, reduction in the frequency of lubricant use and the Schirmer tear function test have been evaluated in clinical trials and are replicable in clinical practice. Most studies had a satisfactory (3 months) treatment and follow-up period.

Ciclosprin has been used as an immunosuppressive agent in a number of conditions. As such, the side-effects and adverse reactions are well-documented. Pre-treatment assessment of patient suitability and on-going post-treatment monitoring are a vital part of current treatment protocol for assessing adverse events. Patient involvement in the choice of treatment is essential as the treatment regime may affect the quality of life. However, as the overall treatment regime is less strenuous than most, patients deem it acceptable.

As the drops are likely to be prescribed to people who have experience in instilling eye drops, there is unlikely to be an issue with application but the patient must be monitored closely due to the potential risk of infection.

In conclusion we feel the prescription of the eye drops should be part of a shared decision making approach. There should be adequate verbal and written

information to support the patient in their decisions. The potential side effects and other treatment choices should be made explicit to the patient.

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.

We are not aware of any additional sources evidence that may not be found via focused systematic review of the available trial evidence.

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)?

Favourable NICE guidance would formalise the use of a technology that is currently used in secondary and tertiary ophthalmic centres for moderate to severe DED. NHS staff would require extra education and training to streamline the indication, prescription, supply and administration of the technology. Please also note our earlier comments about shared decision making.

If care were to be devolved to advanced allied health care professionals, additional training and service set-up would also be required.

In the short term, NHS services that currently use the technology should not require any additional hard infrastructure. However, the continued use of the technology may lead to service expansion with the accompanying requirements.

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Equality

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.

We feel that in line with the summary of product characteristics for the technology, care should be taken before commencing treatment in pregnant women and nursing mothers due to the potential risk to the foetus/infant.

Another potential issue lies with the availability of this important technology if it were not recommended by NICE. A circumstance of "postcode lottery" may arise if the treatment is deemed to be safe and effective in moderate to severe DED, but decision to use it is considered optional and subject to monetary outcomes rather than in the interest of patient satisfaction and quality of life outcomes.

[i] Kheirkha A, Zavareh MK, Farzbod F, Mahbod M, Behrouz MJ (2011) Topical).005% tacrolimus eye drop for refractory vernal keratoconjunctivitis. Eye, London 25: pages 872 – 880

[ii] Huang JF, Yafawi R, Zhang M (2012) Immunodolatory effect of the topic ophthalmic Janus kinase inhibitor tofacitinib (CP-690, 500) in patients with dry eye disease. Ophthalmology 119 pages 43-50