NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Everolimus for preventing organ rejection in liver transplantation

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: [redacted]

Name of your organisation University of Birmingham/University Hospital Birmingham NHS 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.)? √
- 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? 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?

Across the UK there is broad consensus and most patients will receive a combination of Tacrolimus, an anti-metabolite (Azathioprine/MMF) and steroids.

Patients at higher risk of renal dysfunction may receive induction therapy which include monoclonal antibodies or intravenous MMF to allow for delayed introduction of Tacrolimus. There is variation across liver units in use of induction regimens, choice of anti-metabolites and duration of treatment with anti-metabolites/steroids.

There are some differences in professional opinion covering choice of anti-metabolite, use of generic CNI and long-term value of additional anti-metabolite usage.

Another strategy to reduce renal dysfunction has been a move towards minimising dose of Tacrolimus (and other CNIs such as Cyclosporin), although there is variation in how this is achieved.

Sirolimus is used by some units to achieve CNI minimisation although its use varies quite significantly across units.

The potential advantage of Everolimus may be to preserve renal function. There are ongoing discussions about use of generic Tacrolimus which may potentially reduce NHS costs. In addition, prescribing of CNIs (Tacrolimus) is being repatriated to Liver Units which may also influence decisions around use of generic CNIs.

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?

Yes. There are recognised groups of patients that have different prognosis following a liver transplant, and in particular in relation to levels of renal dysfunction. Some examples are included below:

- Patients receiving Donation after Cardiac Death (DCD) liver transplants
- Patients receiving a second (or subsequent) liver graft
- Patients receiving a transplant for acute liver failure
- Patients undergoing combined transplantation with an organ additional to liver
- Patients with renal dysfunction
- Patients with chronic hepatitis C infection (although this may change in the light of new anti-viral therapies becoming available)

Thus, groups may benefit differently from Everolimus.

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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)?

This technology will only be relevant in secondary care/specialist clinics as prescribing is being repatriated to liver units. No real impact on other HCPs.

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?

Not available.

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.

There are no relevant guidelines regarding use of immunosuppressant medications in the setting of UK liver transplantation.

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?

Its usage will be determined by the nature of the supporting data and evaluation by NICE. If a new therapy can demonstrate preservation of renal function without compromising graft function it would be used. This will need to be weighed against additional cost and/or need for additional monitoring. With any new treatment there is commonly a lack of long-term data which may impact on usage.

The regimen is more complicated than current therapy and will likely require additional monitoring. There is also potential for additional/new drug interactions which health care professionals will need to become familiar with. Similarly there may be an additional burden to patients in terms of additional medications needed.

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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.

Starting rules will be informed by submission documents and evaluation by NICE. It will be important that there is clarity on the introduction of a new therapeutic agent. Similarly the use of stopping rules may be relevant if for example there is no demonstrable effect after introduction.

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?

Yes, the use of Everolimus in the published clinical studies reflects how it would be used in the UK. 49.5% of patients in the Everolimus arm had stopped taking study drug within the first 11 months as opposed to 38.2% in the standard CNI arm. The important outcomes that were measured were renal function post-transplant, which missed the primary end-point in the index study, although in extension studies was significant. Need for renal replacement therapy or kidney transplantation are robust measures of the impact of renal dysfunction but as far as I could see these were not in the extension manuscript. Treatment failure as defined by biopsy proven acute rejection (BPAR), graft loss, death or loss to follow-up was higher with Everolimus after 11 months but not different after 3 years.

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?

Peripheral oedema, back pain and hypercholesterolaemia were more common in Everolimus patients although nausea was better. These effects may well impact negatively on patients quality of life and hypercholesterolaemia may have longer term effects on cardiovascular disease. I'm not aware of any subsequent adverse events that have become apparent since the clinical trials were reported.

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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;

No

- 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;

No

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

No

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

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.

No, all necessary information should be found by the systematic review.

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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)?

Extra education and training would not be required as the monitoring would be driven by specialist liver units that have all the relevant expertise. There may be additional testing costs.