NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Everolimus for preventing organ rejection in liver transplantation

Draft scope (pre-invite)

Remit/Appraisal objective

To appraise the clinical and cost effectiveness of everolimus within its licensed indication for preventing organ rejection in allogeneic liver transplantation.

Background

Liver failure occurs when the liver is unable to repair itself and maintain its normal function. Liver failure can be caused by drug toxicity (for example, after paracetamol overdose), viral hepatitis infection, autoimmune liver disease, alcohol-related liver disease, non-alcoholic fatty liver disease, and biliary cirrhosis (a disease that damages the small bile ducts in the liver). Symptoms of a failing liver include a loss of appetite, yellowing of the skin, itching, loss of muscle and weight, and passing of black stools. For people with liver failure, liver transplantation using an organ from a human donor (allogeneic transplant) may be considered. Allogeneic liver transplantation can also be used to treat hepatocellular carcinoma (a type of liver cancer). However, the recurrence of cancer can shorten survival of the transplanted organ.

Between April 2012 and March 2013, 628 liver transplantations were performed in England. About 8000 people in the UK have a functioning liver transplant.

After a liver transplant, life-long treatment with immunosuppressant drugs is needed to prevent rejection of the transplanted organ (or 'graft'). Immunosuppressive regimens often begin with a short induction phase, usually with monoclonal or polyclonal antibodies, followed by initial and then long-term maintenance treatment. Initial maintenance treatment usually comprises triple therapy with a calcineurin inhibitor (such as ciclosporin or tacrolimus), a corticosteroid (prednisolone), and an anti-proliferative agent (such as azathioprine, mycophenolic acid or occasionally sirolimus). Mycophenolic acid is available in 2 formulations called mycophenolate mofetil and mycophenolate sodium. Long-term maintenance therapy is often the same as initial maintenance therapy, but with a reduced dose.

The aim of immunosuppressant therapy is to reduce the risk of organ rejection whilst minimising the adverse effects of treatment. The adverse effects of long-term immunosuppressant therapy include impaired kidney function, higher risk of cardiovascular disease, infections, osteoporosis, and cancer.

The technology

Everolimus (Certican, Novartis Pharmaceuticals) is an immunosuppressant analogue of sirolimus that inhibits the mammalian target of rapamycin (mTOR) protein. It acts as an antiproliferative and is administered orally.

Everolimus does not currently have a UK marketing authorisation for preventing organ rejection in liver transplantation. It has been studied in a clinical trial in adults who had recently received an allogeneic liver transplant. The trial compared a regimen of everolimus plus a tapering dose of tacrolimus and a corticosteroid with a regimen of standard-dose tacrolimus and a corticosteroid. In the trial, everolimus was used as a maintenance therapy rather than an induction therapy.

Intervention(s)	Everolimus in combination with a calcineurin inhibitor and a corticosteroid
Population(s)	People undergoing allogeneic liver transplantation
Comparators	Standard immunosuppressive therapy with a calcineurin inhibitor (such as ciclosporin or tacrolimus) and a corticosteroid, in combination with: • azathioprine; **or** • mycophenolic acid.
Outcomes	The outcome measures to be considered include: • patient survival • graft survival • graft function • graft fibrosis • time to acute rejection • time to recurrence of hepatocellular carcinoma • renal function • time to end-stage renal disease • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows, the use of everolimus in treatment strategies that reduce or withdraw calcineurin inhibitors or corticosteroids will be considered. If evidence allows, the following subgroups will be considered: • people with hepatitis C infection • people with renal dysfunction. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	Related Guidelines: Clinical Guideline No. 100, Jun 2010, Alcohol-use disorders: Diagnosis and clinical management of alcohol-related physical complications. Review proposal date to be confirmed. Clinical Guideline No. 135, Dec 2011, Organ donation for transplantation: improving donor identification and consent rates for deceased organ donation. Review proposal date to be confirmed. Related Interventional Procedures: Interventional Procedure Guidance No. 194, Nov 2006, Living-donor liver transplantation. Related NICE Pathway: Alcohol-use disorders, Pathway created May 2011. http://pathways.nice.org.uk/pathways/alcohol-use-disorders/alcohol-use-disorders-overview
Related National Policy	NHS England Manual for Prescribed Specialised Services 2013/14. 69. Liver transplantation service (adults and children) [page 162]: http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf

Questions for consultation

Have all relevant comparators for everolimus been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for preventing organ rejection in allogeneic liver transplantation?

- Should sirolimus be included as a comparator? If so, which drugs are typically used in combination with sirolimus in the NHS for preventing organ rejection in liver transplantation?

In clinical practice, is everolimus likely to be used in combination with any calcineurin inhibitor, or only with tacrolimus?

- Will everolimus be used in combination with immediate-release tacrolimus or prolonged-release tacrolimus?

- Is it likely to be used in combination with ciclosporin?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom everolimus is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider everolimus will fit into the existing NICE pathway on alcohol-use disorders?

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 the draft scope may need changing in order to meet these aims. In particular, please tell us if the draft scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which everolimus 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 everolimus;

- could 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.

Do you consider everolimus to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of everolimus can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.