NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA348; Everolimus for preventing organ rejection in liver transplantation

Original publication date:	22 July 2015
Review date	July 2018
Existing recommendations:	Not recommended To see the complete existing recommendations and the original remit for TA348, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

New clinical evidence has been identified that is relevant to this appraisal.

The extension of study H2304[1,2] in adult deceased donor liver transplantation recipients, a key study included in the original guidance, confirmed a smaller decrease in estimated glomerular filtration rate (eGFR) associated with everolimus and reduced-dose tacrolimus compared with standard tacrolimus, .[3] However, a new study in adult living donor liver transplantation recipients did not find statistically significant benefits in change of eGFR and biopsy proven acute rejection (BPAR) for everolimus and reduced-dose tacrolimus compared with standard tacrolimus at 12 months follow-up (H2307 study)[4]. Similarly, 2 abstracts reported no difference in the incidence of clinically suspected acute rejection, and found some significant mean eGFR changes in first-time liver-transplant recipients receiving everolimus with reduced-dose tacrolimus, compared with tacrolimus and mycophenolate mofetil (REDUCE study).[5,6]

In addition, a recent Cochrane systematic review concluded that there is no difference amongst maintenance immunosuppressive regimens for mortality, graft loss, adverse events, re-transplantation, and acute graft rejections.[7]

Although this new evidence may result in small changes to the clinical effectiveness estimates, it is unlikely that it would influence the cost-effectiveness results significantly, or lead to a change in the recommendation in TA348.

3. Summary of new evidence and implications for review

Original guidance:

The key trial was H2304 (n=719; NCT00622869), a multicentre, open-label randomised controlled trial (RCT) evaluated the efficacy and safety of everolimus in combination with reduced-dose tacrolimus, compared with standard-dose tacrolimus, and with everolimus in combination with tacrolimus elimination in adult deceased donor liver transplantation recipients. Randomisation to the tacrolimus elimination arm was terminated by the Data Monitoring Committee because of a high rate of acute rejections and withdrawals. Results were available for 12-[1] and 24-months[2] follow-up:

- Non-inferiority test was conducted for the primary composite efficacy endpoint: failure rate of treated BPAR, graft loss or death at 12 months post transplantation. Everolimus with reduced-dose tacrolimus was statistically non-inferior to standard-dose tacrolimus alone (*p < 0.001 for non-inferiority*).
- Secondary outcomes were compared for a difference using 2-tailed tests:
    - BPAR: BPAR occurred in 4.1% everolimus and reduced-dose tacrolimus patients compared with 10.7% of standard tacrolimus patients at 12 months (*p = 0.005*).
    - eGFR: everolimus and reduced-dose tacrolimus achieved non-inferiority in change from randomization to month 12 (*p < 0.001 for non-inferiority*), and superiority. The mean eGFR (standard error [SE]) decreased by 2.23 (1.54) mL/min per 1.73 m in everolimus and reduced-dose tacrolimus, and 10.73 (1.54) mL/min per 1.73 m in standard dose tacrolimus (*p < 0.0001*).

Due to a lack of direct evidence, everolimus and reduced-dose tacrolimus was compared with tacrolimus in combination with azathioprine, or mycophenolate mofetil using effectiveness estimates from network meta-analysis (NMA) that included 22 trials. The NMA's result were utilised in the company's health economic models:

- Hepatic model: NMA estimates of BPAR at 3, 6 &12 informed the probability of stable post-transplant acute rejection.
- Renal model: renal dysfunction was measured by decrease in eGFR in 1st year taken from NMA estimates of eGFR.

New evidence:

1. Of people who completed H2304 (n=370), 282 entered a 12-months extension study (H2304 extension; NCT01150097). The smaller decrease in eGFR and less BPAR associated with everolimus and reduced-dose tacrolimus in H2304 remained significant[3]:
    - BPAR: BPAR occurred in 7.3% everolimus and reduced-dose tacrolimus patients compared with 17.7% of standard tacrolimus patients at 36 months (*p = 0.006*).
    - eGFR: From randomization to month 36, everolimus and reduced-dose tacrolimus was associated with a smaller reduction in eGFR. The mean eGFR (standard deviation [SD]) decreased by 7.0 (31.3) mL/min per 1.73 m^2 in everolimus and reduced-dose tacrolimus, and 15.5 (22.7) mL/min per 1.73 m^2 in standard dose tacrolimus (*p = 0.005*).

2. H2307 trial (n=284; NCT01888432), a multicentre, open-label randomised controlled trial in adult living donor liver transplantation recipients comparing everolimus and reduced-dose tacrolimus with standard-dose tacrolimus in adult deceased donor liver transplantation recipients showed non-inferiority in decrease in eGFR with everolimus, but the results were not statistically significantly different between the 2 groups[4]:
   - Composite efficacy endpoint at 12 moths: Everolimus with reduced-dose tacrolimus was statistically non-inferior to standard-dose tacrolimus alone (*p-value for non-inferiority <0.001*).
   - BPAR: BPAR occurred in 4.9% everolimus and reduced-dose tacrolimus patients compared with 4.2% of standard tacrolimus patients at 12 months (the difference was not statistically significant).
   - eGFR: everolimus and reduced-dose tacrolimus achieved non-inferiority in change from randomization to month 12 (*p < 0.001 for non-inferiority*), but not superiority and was similar between groups. The mean eGFR (SE) decreased by 8.0 (1.8) mL/min/1.73 m^2 for everolimus and reduced-dose tacrolimus, and 12.1 (1.8) mL/min/1.73 m^2 in standard dose tacrolimus (p = 0.108).

3. REDUCE (n=291; NCT02040584), an open-label randomised controlled trial, comparing everolimus in combination with reduced-dose tacrolimus, with tacrolimus in combination with mycophenolate mofetil in first-time liver-transplant recipients reported some results in 2 abstracts. The results for intention to treat population of 211 patients showed a statistically significant improvement in eGFR for patients with everolimus and reduced-dose tacrolimus: [5,6]
   - BPAR: there was no difference in the incidence of clinically suspected acute rejection (17.1% with everolimus and reduced-dose tacrolimus, and 15.1% in the control group).
   - eGFR: an increase from 82.2 to 86.1 mL/min/1.73m^2 with everolimus and reduced-dose tacrolimus, and a decrease from 88.4 to 83.2 mL/min/1.73m^2 with tacrolimus in combination with mycophenolate mofetil; with significant mean eGFR changes along the study in patients receiving everolimus.

4. A recent Cochrane systematic review[7] assessed the comparative benefits and harms of different maintenance immunosuppressive regimens in adults undergoing liver transplantation:
   - Based on very low-quality evidence from network meta-analysis, it found no evidence of a difference between different immunosuppressive regimens for mortality, graft loss, adverse events, re-transplantation, and acute graft rejections.
   - It identified 26 RCTs, however, the review had different inclusion and exclusion criteria than the company's review. A number of the studies included in the company's NMA were excluded from the analyses. In addition, it included one study with sirolimus-based regimen and studies comparing cyclosporine with tacrolimus that were not included in the company's analyses. However, the only RCT with everolimus and reduced-dose tacrolimus included in both reviews was H2304.

Implications for review:

In the original guidance, the committee concluded that the ICERs for everolimus with reduced-dose tacrolimus were unlikely to be lower than the company's estimates of £184,000 per QALY gained compared with the mycophenolate mofetil treatment regimen and £107,600 per QALY gained compared with the azathioprine treatment regimen.

The cost of everolimus (Certican) is still the same.

Two new RCTs [4,5,6] investigating the effects of everolimus with reduced-dose tacrolimus in liver transplant were identified. The new evidence, as summarised above for the clinical outputs used in the health-economic model, is similar to the evidence that was available when the original guidance was developed. In addition, a recent Cochrane review[7]concluded that there are no statistically significant differences among maintenance immunosuppressive regimens in adult liver transplantation.

Given the new evidence, it is likely that updating the company's NMA would results in new point estimates. However, the changes are likely to be small, and it is unlikely that it would influence the cost-effectiveness results significantly.

Has there been any change to the price of the technology(ies) since the guidance was published?
No, there have been no changes to the pricing of everolimus (Certican) since the guidance was published.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
In the original guidance TA348, the committee identified several areas of uncertainty, however none of the new studies addressed the issues: • **H2304**: There was uncertainty about how any benefit demonstrated in trial H2304 would translate into clinical practice. • **Network meta-analyses:** There was considerable uncertainty in the results of the network meta-analyses because the dose of tacrolimus was so heterogeneous between the included studies and because the company's approach lacked transparency. It was unclear which studies had been included for the analysis of specific outcomes. – It is unclear how the new evidence would influence the NMA, although updated analyses that are well reported may decrease some of the methodological uncertainty of the NMA. • **Utilities:** The utility estimates for some of the health states were not based on robust evidence (no utilities were collected in H2304 trial). – H2307 did not collect quality of life data.

• **Model structure and stability**: There were concerns about the structure, stability, and complexity of the model. The use of patient-simulation model and the choice of 2 discrete models instead of an integrated model were questioned, because hepatic and renal functions are not entirely independent, and it may not have been the most appropriate design. In addition, it was not possible to identify any key drivers because the company did not undertake deterministic sensitivity analysis. The resulting ICERs were not considered to be robust.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None.

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from August 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

5. Equality issues

No equality issues were raised during the original guidance development.

GE paper sign off: **Helen Knight, 12/07/2018**

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Appendix A – Information from existing guidance

1. Original remit

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

2. Current guidance

1.1 Everolimus is not recommended within its marketing authorisation for preventing organ rejection in people having a liver transplant.

1.2 People whose treatment with everolimus was started within the NHS before this guidance was published, should be able to continue everolimus until they and their NHS clinician consider it appropriate to stop.

3. Research recommendations from original guidance

None

4. Cost information from original guidance

Everolimus (Certican) was available at £148.50, £297.00 and £445.50 for the 0.25 mg, 0.5 mg and 0.75 mg packs respectively, excluding VAT at the time of TA348. The list price has not changed since.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Living-donor liver transplantation (2015) NICE interventional procedures guidance 535

2. Details of new products

No new comparator products were found, however the UKMI Patents Expiry Database [accessed 8th June 2018] reports that the Supplementary Protection Certificate, which guarantees the marketing exclusivity period for everolimus within the EU, expires in July 2018. A paediatric extension to the SPC is also in place which extends the exclusivity period to January 2019. After this generic competition may be anticipated.

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
"Certican is indicated for prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus should be used in combination with tacrolimus and corticosteroids" £148.50, £297.00 and £445.50 for the 0.25 mg, 0.5 mg and 0.75 mg packs respectively, excluding VAT	No change to price or indications. Note that the 0.5mg formulation is no longer listed in the BNF [online, accessed 16th May 2018].

4. Registered and unpublished trials

Trial name and registration number	Details
Efficacy of Everolimus in Combination With Tacrolimus in Liver Transplant Recipients NCT01551212; CRAD001HDE13; 2011-003118-17; HEPHAISTOS	Everolimus + tacrolimus vs. tacrolimus n = 333 Completed in August 2017

Trial name and registration number	Details
De Novo Everolimus Versus Tacrolimus in Combination With Mofetil Mycophenolate and Low Dose Corticosteroids to Reduce Tacrolimus Induced Nephrotoxicity in Liver Transplantation: a Prospective, Multicentric, Randomised Study NCT02909335; 35RC12_8985; 2013-003802-19; FOREVER	n = 180 Not yet recruiting Estimated completion date: November 2021
A 36 Month Multi-center, Open Label, Randomized, Comparator Study to Evaluate the Efficacy and Safety of Everolimus Immunosuppression Treatment in Liver Transplantation for Hepatocellular Carcinoma Exceeding Milan Criteria NCT02081755; 013-307	n = 336 Currently recruiting Estimated completion date: October 2018

5. Relevant services covered by NHS England specialised commissioning

NHS England (2017) Service specification for liver transplantation service in adults. Reference: 170003/S

NHS England (2013) 2013/14 NHS standard contract for live liver transplantation service. Reference: A02/S(HSS)/a

Appendix D – References

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2. Saliba, F., De Simone, P., Nevens, F., De Carlis, L., Metselaar, H.J., Beckebaum, S., Jonas, S., Sudan, D., Fischer, L., Duvoux, C. and Chavin, K.D., 2013. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. *American journal of transplantation*, *13*(7), pp.1734-1745.

3. Fischer, L., Saliba, F., Kaiser, G.M., De Carlis, L., Metselaar, H.J., De Simone, P., Duvoux, C., Nevens, F., Fung, J.J., Dong, G. and Rauer, B., 2015. Three-year outcomes in de novo liver transplant patients receiving everolimus with reduced tacrolimus: follow-up results from a randomized, multicenter study. *Transplantation*, *99*(7), pp.1455-1462.

4. Jeng, L.B., Lee, S.G., Soin, A.S., Lee, W.C., Suh, K.S., Joo, D.J., Uemoto, S., Joh, J., Yoshizumi, T., Yang, H.R. and Song, G.W., 2017. Efficacy and safety of everolimus with reduced tacrolimus in living-donor liver transplant recipients: 12-month results of a randomized multicenter study. *American Journal of Transplantation*.

5. Sanchez-Antolin, G., Gomez-Bravo, M.A., Prieto, M., Llado, L., Otero, A., Serrano, M.T., Jimenez, C., Garcia, M., Santoyo, J. and Navasa, M., 2017, December. Everolimus allows a significant and safe reduction of tacrolimus exposure in the de novo liver transplantation recipients and improves kidney function: 52 weeks data from REDUCE study. In *Hepatology* (Vol. 66, No. 6, Pp. 1259a-1260a). 111 River St, Hoboken 07030-5774, NJ USA: Wiley.

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7. Rodriguez-Peralvarez, M., Guerrero-Misas, M., Thorburn, D., Davidson, B. R., Tsochatzis, E., & Gurusamy, K. S. (2017). Maintenance immunosuppression for adults undergoing liver transplantation: A network meta-analysis. *Cochrane Database of Systematic Reviews*, *3*.