

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

**Immunosuppressive therapy for kidney transplantation in adults (review of
technology appraisal guidance 85) [ID456]**

The following documents are made available to the consultees and commentators:

- 1. Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**
- 2. Consultee and commentator comments on the Appraisal Consultation Document from:**
 - Astellas
 - Cheisi
 - Novartis
 - Sandoz
 - Sanofi
 - Teva
 - British Kidney Patient Association (BKPA)
 - British Transplantation Society (BTS)
 - The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group
- 3. Comments on the Appraisal Consultation Document from experts:**
 - Dr Nicholas Torpey, clinical expert nominated by the British Kidney Patient Association
- 4. Comments on the Appraisal Consultation Document received through the NICE website**
- 5. Assessment Group response to the comments on the ACD**

No comments' responses were received from the Department of Health and NHS England. No comments were received from the patient experts.

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Confidential until publication

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

Response to consultee, commentator and public comments on the Appraisal Consultation Document 2 (post-appeal)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Astellas Pharma Ltd	<p>Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). We have provided our main responses below under the specific ACD consultations questions.</p> <p>Has all of the relevant evidence been taken into account? Given the scope of the appraisal and the methodology used, we consider that no additional evidence has been published relevant to recommendation 1.1 since the response to the ACD in August 2015. Studies are expected to report over the next 12 months, but are not available for the timeline of this appraisal.</p> <p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Given the limitations of the evidence base and the inclusion criteria of the systematic review, we consider that the summaries of clinical and cost-effectiveness are reasonable.</p> <p>Are the recommendations sound and a suitable basis for guidance to the NHS? While we consider the revised recommendations are largely a sound and suitable basis for guidance to the NHS, in order ensure complete guidance is given we recommend the inclusion of the following additional underlined text to recommendation 1.5</p> <p style="padding-left: 40px;">1.5 The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults who:</p> <p style="padding-left: 80px;"><input type="checkbox"/> are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or</p>	<p>Comment noted.</p> <p>Comment noted.</p> <p>Comment noted. The committee understood that the choice between immunosuppressive therapies is influenced by a number factors, including the characteristics and preferences of the person having the treatment, the side effect profiles of the drugs and the risk profile of the donor and recipient. It also recognised that it is important for clinicians to have access to a choice of treatment options to meet the needs of different people. See paragraph 4.2 of the FAD. No change to the FAD.</p>

Consultee	Comment [sic]	Response
	<p><input type="checkbox"/> have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable for example, because of contraindications or intolerance.</p> <p><u>The precise choice of treatment in these patients should be based on clinical judgement taking into account the needs and preferences of the patient</u></p> <p>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We are not aware of any aspects of the recommendations that need consideration with respect to discrimination.</p> <p>Are there any outstanding clinical and commissioning issues that arise during immunosuppressive therapy for kidney transplant for which further guidance is needed? Is there sufficient evidence available that could support the development of additional technology appraisal recommendations to address these issues? Would additional NICE technology appraisal guidance add value, or would other routes be more appropriate to eliminate these issues, such as other NICE programmes or NHS England commissioning policies? Given the reliance on evidence from randomized controlled clinical trials as the basis for guidance to the NHS, we do not consider that there would be value in further work by NICE to develop additional technical appraisal recommendations for immunosuppression in adult renal transplant patients.</p> <p>We consider that an NHS commissioning policy would be a more appropriate route to provide additional guidance to the NHS. This may be assisted by the recent publication of COMMIT guidelines that provide specific practical recommendations for the management of modifiable risks in those kidney transplant patients who have survived the first post-operative year. (ref Neuberger et al 2017 – available here http://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=2017&issue=04002&article=00001&type=abstract, last accessed 8 May 2017)</p>	<p>Comment noted.</p> <p>Comment noted.</p>
Chiesi Ltd	<p>Thank you for the opportunity to comment on the appraisal consultation document (ACD) that was issued on 21st April 2017. In response to the appraisal committee’s specific points of interest, Chiesi would like to comment as follows:</p> <p>Has all of the relevant evidence been taken into account? All evidence within the scope has been taken into account.</p> <p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p>	<p>Comment noted.</p>

Consultee	Comment [sic]	Response
	<p>Despite previous criticism of the modelling methodology, in particular use of acquisition costs, the overall conclusions are reasonable within the scope and products assessed.</p> <p>Are the recommendations sound and a suitable basis for guidance to the NHS? The clinical necessity for both immediate and prolonged release is driven by the urgency post transplant to achieve immunosuppression and to mitigate pharmacodynamic associated side effects. Hence for both clinicians and patients there is a clinical need for medicines with both modalities of release that is not solely reliant on convenience.</p> <p>Chiesi welcome the amendments made to the guidance throughout the consultative process. The recommendations reflect clinical practice in most transplant centres, and enable flexibility for both clinicians and patients, where required.</p> <p>However the recommendations presented in the ACD fail to take account of several important points in relation to the management of kidney transplant in adults within the NHS:</p> <p>The ACD stated that the committee heard from the clinical experts that the choice between immunosuppressive therapies is affected by a number of factors, including the characteristics and preferences of the person having treatment. The committee acknowledged that immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people. The committee understood the value of having a choice of immunosuppressive therapies.</p> <p>Some patients may be unsuitable to receive immediate–release tacrolimus capsules first line including:</p> <ul style="list-style-type: none"> • Those not wishing to ingest animal origin gelatin found in the capsule formulations of tacrolimus , • Those who are allergic to excipients in the preparations included within the scope <p>The recommendations proposed in the ACD do not therefore take account of cases where patients refuse immediate–release tacrolimus, and/or immediate-release tacrolimus is unsuitable as an initial option to prevent organ rejection in adults having a kidney transplant. The current recommendations do not provide any explicit guidance for these patients. However, all these points could be addressed by modification of the recommendations as follows:</p> <p>Immediate-release tacrolimus, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. Treatment should normally be started with the least expensive product. However, treatment can be started with an alternative dosage</p>	<p>Comment noted.</p> <p>Comment noted.</p> <p>Comments noted. The committee recognised that some people may not wish to ingest capsules that contain gelatine for religious or cultural reasons or may be allergic to excipients in particular formulations. Paragraphs 1.2 and 1.3 of the recommendations have been amended to state that treatment should normally be started with the least expensive product but that it can be started with an alternative dosage form if the least expensive product is not suitable (for example if the person is not able to swallow capsules as a result of a disability or they are unable to have a particular excipient because of allergy or religious reasons).</p>

Consultee	Comment [sic]	Response
	<p>form if clinical judgement is that immediate–release capsules are not suitable due to a need to avoid gelatin or an allergy to the excipients.</p> <p>The suggested (or similarly worded) amendments would make the recommendations a sound and suitable basis for guidance to the NHS and thereby ensure that certain groups of patients do not by default receive a treatment that is not suitable for them.</p> <p>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?</p> <p>Some patients due to religious or cultural reasons may be unsuitable to receive immediate–release tacrolimus capsules first line including those not wishing to ingest animal origin gelatin found in the capsule formulations of tacrolimus.^{2,3} This includes those requiring animal origin products to be halal.</p> <p>Are there any outstanding clinical and commissioning issues that arise during immunosuppressive therapy for kidney transplant for which further guidance is needed? Is there sufficient evidence available that could support the development of additional technology appraisal recommendations to address these issues? Would additional NICE technology appraisal guidance add value, or would other routes be more appropriate to eliminate these issues, such as other NICE programmes or NHS England commissioning policies?</p> <p>Chiesi have no comments to this question.</p>	<p>Comment noted. Paragraphs 1.2 and 1.3 of the recommendations have been amended to state that that treatment should normally be started with the least expensive product but that it can be started with an alternative dosage form if the least expensive product is not suitable (for example if the person is not able to swallow capsules as a result of a disability or they are unable to have a particular excipient because of allergy or religious reasons). No further change to the FAD are required.</p> <p>Comment noted.</p>

Consultee	Comment [sic]	Response
	<p>References</p> <p>¹ Enderby et al. Am J Manag Care. 2015; 21:S12-S23</p> <p>¹ Adoport capsules Summary of Product Characteristics Available at: https://www.medicines.org.uk/emc/ [Accessed 18th May 2017]</p> <p>¹ Prograf capsules Summary of Product Characteristics Available at: https://www.medicines.org.uk/emc/ [Accessed 18th May 2017]</p> <p>¹ UK Medicines Information Q&A 381.3. What factors to consider when advising on medicines suitable for a Halal diet? 26th February 2016 Available at: https://www.sps.nhs.uk/articles/how-can-i-find-out-if-medicines-may-be-considered-okoshero-or-ohalalo/ [Accessed 18th May 2017]</p>	
Novartis Pharmaceuticals UK Ltd	<p>Thank you for the opportunity to comment on the second Appraisal Consultation Documents for these appraisals. We welcome the committee's clarification, within both documents, that the recommendations relate solely to initial immunosuppressive therapy, and that no recommendations were possible in patients for whom the recommended therapies are clinically unsuitable.</p> <p>We propose that treatment failure be added to the examples of situations in which the recommended therapies may be clinically unsuitable. Suggested additional text for paragraph 1.5 in both documents is highlighted below;</p> <ul style="list-style-type: none"> • “The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults [children or young people] who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of treatment failure, contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults [children or young people] who: <ul style="list-style-type: none"> ○ are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or ○ have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable for example, because of failure, contraindications or intolerance.” 	<p>Comment noted. The committee recognised that treatment failure is an additional situation in which the recommended therapies may be clinically unsuitable. Paragraph 1.5 of the recommendations has been amended to include treatment failure in addition to contraindications and intolerance.</p>

Consultee	Comment [sic]	Response
	<p>Other minor text clarifications we suggest are as follows:</p> <ol style="list-style-type: none"> At paragraph 4.17 of the latest ACD for ID346 the second sentence refers to Adoport, whereas the third sentence does not. We suggest the third sentence be changed to: "The committee concluded that its preferred analysis used eMIT prices when available and the prices agreed with the Commercial Medicines Unit for Modigraf, Advagraf and Adoport." The same sentence occurs towards the bottom of page 17 of the latest ACD for ID456, and we suggest the same amendment to that document. At paragraph 4.7 of the latest ACD for ID456 there is some duplicate text; "of that of that", which we suggest is removed so that the third sentence reads "The model was independent of that built for NICE's technology appraisal guidance on immunosuppressive therapy for renal transplantation in adults." 	<p>Comment noted. Paragraph 4.7 of the FAD has been amended to include 'Adoport'.</p> <p>Comment noted. The duplicated text has been deleted from the FAD.</p>
Sandoz UK	<p>Sandoz UK would like to thank NICE for the opportunity to provide comments on this appraisal consultation document. We would like to make two comments that could result in benefits for patients.</p> <p><u>Section 3.8, page 7</u> Sandoz UK would like to point out that the strengths and availabilities for Basiliximab (Simulect), Rabbit anti-human thymocyte immunoglobulin (r-ATG), Tacrolimus granules for oral suspension (Modigraf), Prolonged-release tacrolimus (Advagraf), Belatacept (Nulojix), Mycophenolate sodium (Myfortic), Sirolimus (Rapamune) and Everolimus (Certican) are all presented in sections 3.3, 3.6, 3.10, 3.12, 3.16, 3.20, 3.23 and 3.25 respectively. However, in section 3.8, this information has not been presented for the specified brands of immediate-release tacrolimus. Adoport, Capexion, Perixis, Prograf, Tacni, and Vivadex are all available as 0.5mg, 1mg and 5mg tablets. We would like to take the opportunity to highlight that Adoport is available at two additional strengths of 0.75mg and 2mg. Having increased flexibility of Adoport treatment options could facilitate finer and better-balanced daily administration and support the managed dose reductions highlighted in section 3.9. This also allows potential reduction of pill burden.</p> <p><u>Section 4.16, page 23</u> In section 4.16, the committee heard there were no noticeable differences in clinical effectiveness between mycophenolate mofetil and mycophenolate sodium but that the associated QALY gains for mycophenolate sodium, according to available evidence, resulted in this product not being considered cost effective. We would like to notify NICE that the patent for mycophenolate sodium (Myfortic) expires in Q4 2017 after which a number of generic products may come available at a lower cost. Considering guidance for this therapy area will not be reappraised for a further three years after publication of the final document, we are concerned that patients may not benefit from the availability of these potentially cost effective generic products.</p>	<p>Comment noted. Paragraph 3.10 of the FAD has been updated to include the capsule strengths of intermediate-release tacrolimus that are available, in line with other technologies included in the appraisal.</p> <p>Comment noted. The committee considered that a 3 year review date is appropriate for this appraisal. No change to the FAD. Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations; stakeholders</p>

Consultee	Comment [sic]	Response
Sanofi	<p>Thank you for the opportunity to comment on the second Appraisal Consultation Document (ACD) for this appraisal.</p> <p>Our position remains consistent with our previous response to the first ACD but in addition we would be grateful if the Institute could clarify in its final recommendation that the use of rATG in the post-induction setting, treatment of steroid-resistant acute rejection, for preventing organ rejection is outside the remit of the appraisal.</p> <p>We welcome the fact that the Appraisal Committee (AC) were persuaded to consider the evidence from Brennan (2006) during the most recent committee meeting. However, we are concerned that the AC considered only the mean peak panel-reactive antibody levels at the time of transplant as a risk factor when the available evidence clearly shows that risk is multifactorial.</p> <p>We would also like to highlight once again that a significant driver of cost effectiveness is the risk of acute rejection which impacts both quality of life and cost. We believe that the relative risk of rejection has likely been underestimated in the modelling with respect to the comparator and that the incremental cost of prophylaxis for high risk grafts has been overestimated resulting in ICERs for rATG which are high. For these reasons we would request that the evidence constituting risk is considered once again and the AC review their recommendation.</p> <p>Sanofi welcomes the opportunity to respond to the comment on the second Appraisal Consultation Document (ACD) for this appraisal.</p> <p>1. Request for further clarification of the wording in section 1.5. Feedback received by the company from physicians has suggested that the wording to section 1.5 of the recommendation appears to cover the use of rATG to treat steroid-resistant acute rejection in order to save the transplanted organ in patients where the recommended induction treatment has been inadequate. The current wording suggests that rATG has also received a 'Not recommended' status for use in this setting. The use of rATG in this way is beyond the scope of the appraisal and therefore we believe that clinicians would appreciate further clarification from the Institute.</p>	<p>are invited to contact NICE if this arises.</p> <p>Comments noted. See responses to detailed comments below.</p> <p>Comment noted. The guidance states that r-ATG is not recommended as an initial treatment to prevent organ rejection in adults having a kidney transplant; this recommendation applies only to the initial therapy started around the time of transplant. Treatment of episodes of acute rejection is outside the scope of this appraisal and is therefore not referred to in the</p>

Consultee	Comment [sic]	Response
	<p>2. Definition of risk in kidney transplantation.</p> <p>We would like to remind the AC that risk of acute graft rejection does not rest solely with recipient patient factors but that grafts from deceased donors carry risk as well and furthermore combinations of donor and recipient risk are important. It is therefore essential to characterise risk as overall graft risk which does not necessarily reside only with recipients and we believe that the Brennan study (2006) is the best data to capture and describe the outcomes of procedures for high risk grafts.</p> <p>The first ACD acknowledged that rATG may be beneficial in high risk patients but stated that there is insufficient evidence on which to base specific recommendations for this population. During the most recent committee meeting the AC noted that the mean peak panel-reactive antibody was approximately 14% in both groups in the Brennan (2006) study, with a mean value of about 6% at the time of transplant and this formed that basis of their conclusion that these patients were not at high immunological risk. We would like to reiterate that the KDIGO guidelines state that cases where PRA is above 0% are considered high risk and in these cases rATG is recommended.</p> <p>Sanofi continues to believe that there is robust evidence available to support a recommendation for rATG in grafts at high risk of acute rejection as described in the Brennan study.</p> <p>Of note Brennan shows that are different rates of antibody treated acute rejection for the basiliximab (8.0%) and rATG (1.4%) arms. Treatment at this stage is usually with rATG but the economic model does not incorporate such a difference because this evidence for high risk grafts is not modelled separately. The costs incorporated in the economic model arise from a study by Ling, Pandit and Bennett in which the additional cost for failure is described as £3,557.39. This study is not publically available and we believe this represents an underestimation of the true costs. For example a recent study in German patients has estimated the cost for patients experiencing non-fatal graft failure at €[REDACTED]. (Cremasch, <i>accepted for publication</i>) Taken together more appropriate rates and costs are likely to result in improved ICERS for rATG.</p> <p>Finally we would also like to reiterate that grafts at high risk are likely to receive similar rates of prophylaxis regardless of the therapy and that the most appropriate data to use for this is once again that taken from Brennan where the outcomes favour rATG for CMV infection rate. This is not reflected in the current model which incorporates greater cost in the rATG arm due to prophylaxis resulting in probable overestimation of the ICERS.</p>	<p>recommendations. No change is required.</p> <p>Comments noted. The committee understood that the risk profile of the kidney donor and recipient are important considerations when choosing immunosuppressive therapy, and that immunological risk is influenced by a number of factors as well as panel-reactive antibody levels (paragraphs 4.2 and 4.11). It is acknowledged that the KDIGO guideline states that the risk factors for acute rejection include a panel-reactive antibody level of greater than 0%.</p> <p>The committee discussed the Brennan (2006) study in detail and was aware that this study enrolled people at risk of delayed graft function or acute rejection (and not necessarily people with high immunological risk. It is acknowledged that rates of antibody-treated acute rejection and CMV infection differed between the basiliximab and r-ATG groups in this study. The committee noted that the appeal panel recognised that the committee was required to make a decision that weighted imperfect clinical trial evidence against unsystematic clinical experience. The appeal panel noted that, insofar as the committee were able to analyse the data, r-ATG was</p>

Consultee	Comment [sic]	Response
	<p>References Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D; Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. <i>N Engl J Med</i> 2006;355:1967-77. KDIGO: Kidney Disease Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. <i>American Journal of Transplantation</i> 2009;9:S1–S157. Cremaschi L, von Versen, R, Benzing T, Wiesener M, Zink N, Milkovich N, Paivanas T, Gallagher M, Thaiss F, 'Induction therapy with rabbit antithymocyte globulin versus basiliximab after kidney transplantation: A health economic analysis from a German perspective' <i>Accepted for publication in Transplant International</i>.</p>	<p>unlikely to cost-effective or superior to basiliximab. The committee noted that the appeal panel concluded that it was not unreasonable for the committee to decide, on that basis, that r-ATG should not be recommended. The committee concluded that it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups, and in particular there was not enough evidence to support recommendations in people with high immunological risk (see paragraphs 4.8 and 4.11). The committee further concluded that r-ATG was not cost-effective for preventing organ rejection in adults having a kidney transplant (paragraph 4.11).</p>
Teva UK Limited	<p>Many thanks for giving us the opportunity to comment on the appraisal consultation document.</p> <p>Our only comment is around the proposed date of review. With ongoing changes to product availability and licenses as new products are approved, we feel that it would be more pertinent to consider for review after 2 years rather than waiting for 3 years before a formal review as stated in the document.</p>	<p>Comment noted. The committee considered that a 3 year review date is appropriate for this appraisal. No change to the FAD. Guidance may be reviewed before the suggested review time when there is significant new evidence that is likely to change the recommendations; stakeholders are invited to contact NICE if this arises.</p>

Consultee	Comment [sic]	Response
<p>British Kidney Patient Association</p>	<p>The British Kidney Patient Association (BKPA) is a national charity which works to improve quality of life for kidney patients through advocacy, direct grants, educating and informing patients, counselling and funding patient-centred research, healthcare professionals and projects.</p> <p>The BKPA was extremely concerned about the previously proposed multiple technology appraisal on immunosuppressant therapies, which recommended that just 3 drugs (basiliximab, immediate-release tacrolimus and mycophenolate mofetil) should be used to prevent rejection of a kidney transplant.</p> <p>The appraisal did not take account the impact of the recommendations on patients who may be unable to tolerate the recommended drugs, thereby making up to 20% of transplants likely to fail. It also had the potential to affect second or subsequent transplants when access to the range of drugs might be even more important if problems had developed with the three drugs.</p> <p>We note that the revised recommendations in 1.5 go some way to recognising this issue:</p> <p>1.5 The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults who:</p> <ul style="list-style-type: none"> • are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or • have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable for example, because of contraindications or intolerance. 	<p>Comment noted.</p>

Consultee	Comment [sic]	Response
	<p>We would like to thank the patient experts from our patient advisory group who attended the recent committee meeting. We hope that this revised guidance will allow sufficient flexibility for prescribing of currently commissioned immunosuppression agents (listed in 1.4) where clinical indications exist; we are encouraged that NICE accepted the points we made in our submissions to the appeal meeting in April 2016.</p> <p>We note the reference to 'haemodialysis' three times on page 25 in the revised consultation document and request that this is amended to state 'dialysis' as patients may choose to go onto either haemo or peritoneal dialysis and have the right to chose the therapy which suits them. The revised consultation makes it clear that both clinical and patient experts believe that a successful transplant offers the opportunity for an improved quality of life. We believe that the conclusions could be clearer on the costs in quality of life and side effects as well as costs to the system of the patient returning to dialysis if a transplant fails (dialysis is estimated at £30,800 pa not including transport costs, certain drugs, and the cost to carers http://www.england.nhs.uk/wp-content/uploads/2014/04/a07-renal-transpl-ad-0414.pdf and the costs of a failed transplant at £17,000).</p>	<p>Comment noted.</p> <p>Comment noted. Text changed from 'haemodialysis' to 'dialysis'. The committee was aware that returning to dialysis if a transplant fails can have a significant effect on quality of life as well as incurring costs to the NHS. See paragraph 4.20 of the FAD.</p>
British Transplantation Society	<p>The British Transplantation Society (BTS) notes the ACD in response to the appeal process to the preliminary guidance (ID456) and welcomes the changes that have been made following the appeal hearing in March 2016. We endorse the response of our clinical expert and representative, Dr Nicholas Torpey, who has been closely involved throughout the process.</p> <p>Specifically, we endorse:</p> <p>The statements in section 4.20 of the guidance that clarify:</p> <ul style="list-style-type: none"> - The scope of the evidence and its application to immunosuppressive therapy given at the time of transplant - The relevance of recommendations 1.1-1.4 to initial therapy only. - That there are patients who will not tolerate the recommended therapy and that consideration of the management of these patients was beyond the scope of the original Assessment Group <p>We also endorse the proposal made by Dr Torpey about inclusion of a specific sentence to clarify the evidence to support ensuring that alternative, effective immunosuppressive therapy is made available to patients who are intolerant to calcineurin inhibitors (page 25). Such decisions are time-sensitive and appropriate funding mechanisms must be in place to facilitate effective changes in immunosuppressive therapy when individual patients require it.</p>	<p>Comment noted.</p> <p>Comment noted.</p> <p>Comment noted. The committee noted the evidence on the effect of withdrawing tacrolimus; see paragraph 4.20 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>In the interests of patient choice and to promote concordance, we support the inclusion of slow release tacrolimus in the recommendations if cost effective preparations can be sourced (3.12 and 4.13).</p>	<p>Comment noted. The committee considered that prolonged-release tacrolimus was not cost effective, based on the evidence (and prices) it had seen. No changes to FAD.</p>
<p>ESPRIT</p>	<p>As an independent group, the ESPRIT Group (www.esprit.org.uk) does not advocate any particular product and our opinions, recommendations and activities are all our own. As such we could not contribute to NICE's assessment of the <i>comparative</i> efficacy and cost-effectiveness of individual immunosuppressants included in the MTA. However, where the efficacy and safety of treatment of transplant patients is potentially threatened, we feel it of vital importance to highlight our concerns and the principles underlying them. This underpinned all the various arguments which we presented as part of the Appeal process following the last FAD.</p> <p>Overall we were pleased with the provisions of this ACD and consider the latest recommendations to be sound and a suitable basis for guidance to the NHS. In particular we welcome:</p> <ul style="list-style-type: none"> • That the recommendations clearly only apply to the initial period of immunosuppression after transplantation • It is reasonable that NICE is 'unable to make recommendations' for patients who are, or become, unable to have the recommended initial agents or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid. This reflects the importance of maintaining flexibility for experienced transplant professionals to provide tailored immunosuppression in line with the varying needs of individual transplant patients • That it clearly states the recommendations are not intended to affect treatment with any technologies started in the NHS before the guidance is published - i.e. does not affect patients who are already being managed on clinically-tailored regimens - and clearly states that funding for these patient treatments should continue <p>We are in agreement with the proposal that the guidance gets reviewed again in three years.</p>	<p>Comment noted.</p> <p>Comment noted</p> <p>Comment noted.</p>

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
British Transplant Society	<p>Thank you for the opportunity to comment on this ACD. I have been involved in the evolution of this Multiple Technologies Assessment Guideline (MTAG) in several capacities, including:</p> <ul style="list-style-type: none"> • As a member of the British Transplant Society (BTS) Council – responding to earlier versions of this appraisal • Representing the BTS, Renal Association and British Renal Society at the Appeal hearing in March 2016 • As a clinical expert at the Appraisal Group committee meeting in March 2017 <p>I have read the current ACD (April 2017) carefully and the comments below are my own views as an invited clinical expert. I have also discussed the ACD with my colleagues at the BTS, shared my views, and contributed to the BTS response made separately.</p> <p>Overall, I believe the current ACD fairly reflects the points that the committee were asked to address following the appeal hearing in March 2016. There are several key points:</p> <ol style="list-style-type: none"> 1. Most importantly, there is now a clear statement that the evidence considered by the Assessment Group (AG) and used to inform this ACD is restricted to immunosuppression <i>given at the time of transplantation (both induction and maintenance treatment)</i> – section 4.20 - and that the recommendations summarized in points 1.1 – 1.4 apply only to such <i>initial treatment</i>. 2. Secondly, there is now a clear statement that a <i>significant cohort of patients will not tolerate the recommended initial treatment - section 4.20</i> - and that evidence regarding the management of immunosuppression in these patients was not considered by the AG nor forms part of this appraisal – reflected in recommendation 1.5 and in the last sentence of section 4.20. 3. Perhaps the key clinical issue is the management of patients intolerant of calcineurin inhibitors (tacrolimus and ciclosporin). At the committee meeting in March 2017 I drew attention to two recent clinical studies in which tacrolimus was deliberately withdrawn from an immunosuppressive regimen almost identical to that recommended in this ACD. Both trials were terminated early by data monitoring committees because of an unacceptable rate of rejection following tacrolimus withdrawal^{1,2}. These reports emphasize the need for alternative immunosuppressive options for those patients unable to continue with calcineurin inhibitors. Would it be useful to include a comment such as ‘<i>a clinical expert drew attention to recent trials emphasizing the requirement for</i> 	<p>Comment noted.</p> <p>Comment noted.</p> <p>Comment noted. The committee noted the evidence on the effect of withdrawing tacrolimus; see paragraph 4.20 of the FAD.</p>

Nominating organisation	Comment [sic]	Response
	<p><i>effective alternative immunosuppression in those patients intolerant of calcineurin inhibitors</i>’ in addition to the sentence beginning on line 10, page 25</p> <p>4. Section 4.20 is quite long. Would it be reasonable to split it into 2 parts at the point identified above (line 12, page 25)? I think it would be useful in the second section – which is a helpful discussion on the alternatives to calcineurin inhibitors – to clarify the point that there is a significant and recognizable <i>cohort</i> of patients for whom alternatives to calcineurin inhibitors may be required. Accordingly the current NHSE system for Individual Funding Requests (IFR) that requires ‘exceptionality’ is <i>clearly</i> inappropriate. The final sentence (page 26, lines 5-9) is critically important, emphasizing recommendation 1.5.</p> <p>5. Section 1.2 refers specifically to Modigraf (tacrolimus granules), indicating that Modigraf may be used if available at an agreed cost. My recollection from the appeal hearing is that, after some discussion, there was acknowledgement that prolonged release tacrolimus (Advagraf) was equally effective as twice daily preparations, but more expensive (sections 3.12 and 4.13). Would it be reasonable to add a statement indicating that prolonged release tacrolimus is an acceptable alternative to standard release preparations if available at equivalent cost?</p> <p>References</p> <p>1. Dugast E, Souillou J-P, Foucher Y et al (2016). Failure of calcineurin inhibitor (tacrolimus) weaning randomized trial in long-term stable kidney transplant recipients. <i>Am J Transplant</i> 16: 3255-3261.</p> <p>2. Hricik D, Formica R, Nickerson P et al (2015). Adverse outcomes of tacrolimus withdrawal in immune-quiescent kidney transplant recipients. <i>J Am Soc Nephrol</i> 26: 3114-3122.</p>	<p>Comment noted. The addition of the new sentence to paragraph 4.20 highlighting the available evidence on tacrolimus withdrawal points to a group of people who need alternative immunosuppressants if treatment with tacrolimus needs to be stopped. No further change to the FAD.</p> <p>Comment noted. The committee had previously recommended all forms of immediate-release tacrolimus, taking into account the costs of all the formulations. Modigraf is included in paragraph 1.2 to highlight treatment options for people who are unable to have other formulations of immediate-release tacrolimus (for example, people who are unable to swallow capsules as a result of a disability or unable to have a particular excipient because of religious reasons). The committee considered that prolonged-release tacrolimus was not cost effective, based on the evidence (and prices) it had seen. No changes to the FAD.</p>

Confidential until publication

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS professional	General	rATG has been acknowledged to be clinically effective as are many other immunosuppressants that are part of this review namely, prolonged release tacrolimus and belatacept. What the review does not adequately capture or account for is increased risk of graft loss due to non-adherence leading morbidity and increased mortality associated with return to dialysis. Every clinical decision even though not cost effective is made based on the risk and balance of mortality on dialysis versus prolonging transplant graft function. Belatacept is likely to be cost effective if the reduced incidence of MI, CVA and drugs used to treat hyperlipidemia, NODAT, increased hospital visits due to these complications are all taken in to account.	Comments noted. The committee considered that the induction and maintenance therapies included in this appraisal are effective treatment options (see paragraphs 4.5 and 4.6). The economic model included the costs and effects of returning to dialysis, cardiovascular disease and NODAT. No changes to the FAD are needed.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.



Astellas Pharma Limited Response – 16 May 2017

NICE Appraisal Consultation Document - Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). We have provided our main responses below under the specific ACD consultations questions.

Has all of the relevant evidence been taken into account?

Given the scope of the appraisal and the methodology used, we consider that no additional evidence has been published relevant to recommendation 1.1 since the response to the ACD in August 2015. Studies are expected to report over the next 12 months, but are not available for the timeline of this appraisal.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Given the limitations of the evidence base and the inclusion criteria of the systematic review, we consider that the summaries of clinical and cost-effectiveness are reasonable.

Are the recommendations sound and a suitable basis for guidance to the NHS?

While we consider the revised recommendations are largely a sound and suitable basis for guidance to the NHS, in order ensure complete guidance is given we recommend the inclusion of the following additional underlined text to recommendation 1.5

1.5 The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults who:

- are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or
- have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable for example, because of contraindications or intolerance.



The precise choice of treatment in these patients should be based on clinical judgement taking into account the needs and preferences of the patient

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We are not aware of any aspects of the recommendations that need consideration with respect to discrimination.

Are there any outstanding clinical and commissioning issues that arise during immunosuppressive therapy for kidney transplant for which further guidance is needed? Is there sufficient evidence available that could support the development of additional technology appraisal recommendations to address these issues? Would additional NICE technology appraisal guidance add value, or would other routes be more appropriate to eliminate these issues, such as other NICE programmes or NHS England commissioning policies?

Given the reliance on evidence from randomized controlled clinical trials as the basis for guidance to the NHS, we do not consider that there would be value in further work by NICE to develop additional technical appraisal recommendations for immunosuppression in adult renal transplant patients.

We consider that an NHS commissioning policy would be a more appropriate route to provide additional guidance to the NHS. This may be assisted by the recent publication of COMMIT guidelines that provide specific practical recommendations for the management of modifiable risks in those kidney transplant patients who have survived the first post-operative year. (ref Neuberger et al 2017 – available here <http://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=2017&issue=04002&article=00001&type=abstract>, last accessed 8 May 2017).

Regards,

[Redacted signature block]

Kate Moore
Technology Appraisals Project Manager - Committee D
National Institute for Health and Care Excellence

22nd May 2017

**Multiple Technology Appraisal Kidney transplantation (adults) -
immunosuppressive therapy (review of TA 85) [ID456]**

Dear Kate,

Re: Company Response to Appraisal Consultation Document

Thank you for the opportunity to comment on the appraisal consultation document (ACD) that was issued on 21st April 2017. In response to the appraisal committee's specific points of interest, Chiesi would like to comment as follows:

Has all of the relevant evidence been taken into account?

All evidence within the scope has been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Despite previous criticism of the modelling methodology, in particular use of acquisition costs, the overall conclusions are reasonable within the scope and products assessed.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The clinical necessity for both immediate and prolonged release is driven by the urgency post transplant to achieve immunosuppression and to mitigate pharmacodynamic associated side effects. Hence for both clinicians and patients there is a clinical need for medicines with both modalities of release that is not solely reliant on convenience.¹

Chiesi welcome the amendments made to the guidance throughout the consultative process. The recommendations reflect clinical practice in most transplant centres, and enable flexibility for both clinicians and patients, where required.

However the recommendations presented in the ACD fail to take account of several important points in relation to the management of kidney transplant in adults within the NHS:

The ACD stated that the committee heard from the clinical experts that the choice between immunosuppressive therapies is affected by a number of factors, including the characteristics and preferences of the person having treatment. The committee acknowledged that immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people. The committee understood the value of having a choice of immunosuppressive therapies.

Some patients may be unsuitable to receive immediate–release tacrolimus capsules first line including:

- Those not wishing to ingest animal origin gelatin found in the capsule formulations of tacrolimus^{2,3}
- Those who are allergic to excipients in the preparations included within the scope

The recommendations proposed in the ACD do not therefore take account of cases where patients refuse immediate–release tacrolimus, and/or immediate-release tacrolimus is unsuitable as an initial option to prevent organ rejection in adults having a kidney transplant. The current recommendations do not provide any explicit guidance for these patients.

However, all these points could be addressed by modification of the recommendations as follows:

Immediate-release tacrolimus, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in adults having a kidney transplant. Treatment should normally be started with the least expensive product. However, treatment can be started with an alternative dosage

form if clinical judgement is that immediate-release capsules are not suitable due to a need to avoid gelatin or an allergy to the excipients.

The suggested (or similarly worded) amendments would make the recommendations a sound and suitable basis for guidance to the NHS and thereby ensure that certain groups of patients do not by default receive a treatment that is not suitable for them.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Some patients due to religious or cultural reasons may be unsuitable to receive immediate-release tacrolimus capsules first line including those not wishing to ingest animal origin gelatin found in the capsule formulations of tacrolimus.^{2,3} This includes those requiring animal origin products to be halal.⁴

Are there any outstanding clinical and commissioning issues that arise during immunosuppressive therapy for kidney transplant for which further guidance is needed? Is there sufficient evidence available that could support the development of additional technology appraisal recommendations to address these issues? Would additional NICE technology appraisal guidance add value, or would other routes be more appropriate to eliminate these issues, such as other NICE programmes or NHS England commissioning policies?

Chiesi have no comments to this question.

If you or the Appraisal Committee have any queries regarding Chiesi's comments on the ACD or if anything is unclear, then please do not hesitate to contact me. I look forward to seeing you at the next Appraisal Committee meeting.

Yours faithfully,

[Redacted signature block]

Chiesi Limited

References

¹ Enderby et al. Am J Manag Care. 2015; 21:S12-S23

² Adoport capsules Summary of Product Characteristics
Available at: <https://www.medicines.org.uk/emc/> [Accessed 18th May 2017]

³ Prograf capsules Summary of Product Characteristics
Available at: <https://www.medicines.org.uk/emc/> [Accessed 18th May 2017]

⁴ UK Medicines Information Q&A 381.3. What factors to consider when advising on medicines suitable for a Halal diet? 26th February 2016
Available at: <https://www.sps.nhs.uk/articles/how-can-i-find-out-if-medicines-may-be-considered-okoshero-or-ohalalo/> [Accessed 18th May 2017]

Novartis Pharmaceuticals UK Ltd
Frimley Business Park
Frimley
Camberley
Surrey GU16 7SR

Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza
Manchester
M1 4BT

22nd May 2017

Dear Mr Boysen,

Re: Novartis response to the second Appraisal Consultation Document for ID346 & ID 456

Thank you for the opportunity to comment on the second Appraisal Consultation Documents for these appraisals. We welcome the committee's clarification, within both documents, that the recommendations relate solely to initial immunosuppressive therapy, and that no recommendations were possible in patients for whom the recommended therapies are clinically unsuitable.

We propose that treatment failure be added to the examples of situations in which the recommended therapies may be clinically unsuitable. Suggested additional text for paragraph 1.5 in both documents is highlighted below;

- “The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults [children or young people] who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of **treatment failure**, contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults [children or young people] who:
 - are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or
 - have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable for example, because of **failure**, contraindications or intolerance.”

Other minor text clarifications we suggest are as follows:

1. At paragraph 4.17 of the latest ACD for ID346 the second sentence refers to Adoport, whereas the third sentence does not. We suggest the third sentence be changed to: “The committee concluded that its preferred analysis used eMIT prices when

available and the prices agreed with the Commercial Medicines Unit for Modigraf, Advagraf **and Adoport.**” The same sentence occurs towards the bottom of page 17 of the latest ACD for ID456, and we suggest the same amendment to that document.

2. At paragraph 4.7 of the latest ACD for ID456 there is some duplicate text; “of that of that”, which we suggest is removed so that the third sentence reads “The model was independent of that built for NICE’s technology appraisal guidance on immunosuppressive therapy for renal transplantation in adults.”

I hope that these comments are helpful.

Yours sincerely,



Name	
Role	Sandoz UK
Other role	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
General	Sandoz UK would like to thank NICE for the opportunity to provide comments on this appraisal consultation document. We would like to make two comments that could result in benefits for patients.
Section 1	
Section 2	
Section 3 (The technologies)	<p><u>Section 3.8, page 7</u></p> <p>Sandoz UK would like to point out that the strengths and availabilities for Basiliximab (Simulect), Rabbit anti-human thymocyte immunoglobulin (r-ATG), Tacrolimus granules for oral suspension (Modigraf), Prolonged-release tacrolimus (Advagraf), Belatacept (Nulojix), Mycophenolate sodium (Myfortic), Sirolimus (Rapamune) and Everolimus (Certican) are all presented in sections 3.3, 3.6, 3.10, 3.12, 3.16, 3.20, 3.23 and 3.25 respectively. However, in section 3.8, this information has not been presented for the specified brands of immediate-release tacrolimus. Adoport, Capexion, Perixis, Prograf, Tacni, and Vivadex are all available as 0.5mg, 1mg and 5mg tablets. We would like to take the opportunity to highlight that Adoport is available at two additional strengths of 0.75mg and 2mg. Having increased flexibility of Adoport treatment options could facilitate finer and better-balanced daily administration and support the managed dose reductions highlighted in section 3.9. This also allows potential reduction of pill burden.</p>
Section 4 (Evidence and interpretation)	<p><u>Section 4.16, page 23</u></p> <p>In section 4.16, the committee heard there were no noticeable differences in clinical effectiveness between mycophenolate mofetil and mycophenolate sodium but that the associated QALY gains for mycophenolate sodium, according to available evidence, resulted in this product not being considered cost effective. We would like to notify NICE that the patent for mycophenolate sodium (Myfortic) expires in Q4 2017 after which a number of generic products may come available at a lower cost. Considering guidance for this therapy area will not be reappraised for a further three years after publication of the final document, we are concerned that patients may not benefit from the availability of these potentially cost effective generic products.</p>
Section 5	
Section 6	
Section 7	
Section 8	



Meindert Boysen
Programme Director, Technology Appraisals
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BD

22nd May 2017

Re: Response to the second ACD for: Kidney transplantation (adults) - immunosuppressive therapy (Review of TA 85) [ID456]

Dear Meindert,

Thank you for the opportunity to comment on the second Appraisal Consultation Document (ACD) for this appraisal.

Our position remains consistent with our previous response to the first ACD but in addition we would be grateful if the Institute could clarify in its final recommendation that the use of rATG in the post-induction setting, treatment of steroid-resistant acute rejection, for preventing organ rejection is outside the remit of the appraisal.

We welcome the fact that the Appraisal Committee (AC) were persuaded to consider the evidence from Brennan (2006) during the most recent committee meeting. However, we are concerned that the AC considered only the mean peak panel-reactive antibody levels at the time of transplant as a risk factor when the available evidence clearly shows that risk is multifactorial.

We would also like to highlight once again that a significant driver of cost effectiveness is the risk of acute rejection which impacts both quality of life and cost. We believe that the relative risk of rejection has likely been underestimated in the modelling with respect to the comparator and that the incremental cost of prophylaxis for high risk grafts has been overestimated resulting in ICERs for rATG which are high. For these reasons we would request that the evidence constituting risk is considered once again and the AC review their recommendation.

Please let me know if you have any questions regarding our comments.

Yours Sincerely,

A black rectangular box redacting the signature of the sender.

Sanofi



Response to the ACD: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Sanofi welcomes the opportunity to respond to the comment on the second Appraisal Consultation Document (ACD) for this appraisal.

1. Request for further clarification of the wording in section 1.5.

Feedback received by the company from physicians has suggested that the wording to section 1.5 of the recommendation appears to cover the use of rATG to treat steroid-resistant acute rejection in order to save the transplanted organ in patients where the recommended induction treatment has been inadequate. The current wording suggests that rATG has also received a 'Not recommended' status for use in this setting. The use of rATG in this way is beyond the scope of the appraisal and therefore we believe that clinicians would appreciate further clarification from the Institute.

2. Definition of risk in kidney transplantation.

We would like to remind the AC that risk of acute graft rejection does not rest solely with recipient patient factors but that grafts from deceased donors carry risk as well and furthermore combinations of donor and recipient risk are important. It is therefore essential to characterise risk as *overall* graft risk which does not necessarily reside only with recipients and we believe that the Brennan study (2006) is the best data to capture and describe the outcomes of procedures for high risk grafts.

The first ACD acknowledged that rATG may be beneficial in high risk patients but stated that there is insufficient evidence on which to base specific recommendations for this population. During the most recent committee meeting the AC noted that the mean peak panel-reactive antibody was approximately 14% in both groups in the Brennan (2006) study, with a mean value of about 6% at the time of transplant and this formed that basis of their conclusion that these patients were not at high immunological risk. We would like to reiterate that the KDIGO guidelines state that cases where PRA is above 0% are considered high risk and in these cases rATG is recommended.

Sanofi continues to believe that there is robust evidence available to support a recommendation for rATG in grafts at high risk of acute rejection as described in the Brennan study.

Of note Brennan shows that are different rates of antibody treated acute rejection for the basiliximab (8.0%) and rATG (1.4%) arms. Treatment at this stage is usually with rATG but the economic model does not incorporate such a difference because this evidence for high risk grafts is not modelled separately. The costs incorporated in the economic model arise from a study by Ling, Pandit and Bennett in which the additional cost for failure is described as £3,557.39. This study is not publically available and we believe this represents an underestimation of the true costs. For example a recent study in German patients has estimated the cost for patients experiencing non-fatal graft failure at €7,239. (Cremasch, *accepted for publication*) Taken together more appropriate rates and costs are likely to result in improved ICERS for rATG.



Finally we would also like to reiterate that grafts at high risk are likely to receive similar rates of prophylaxis regardless of the therapy and that the most appropriate data to use for this is once again that taken from Brennan where the outcomes favour rATG for CMV infection rate. This is not reflected in the current model which incorporates greater cost in the rATG arm due to prophylaxis resulting in probable overestimation of the ICERs.

References

Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D; Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006;355:1967-77.

KDIGO: Kidney Disease Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *American Journal of Transplantation* 2009;9:S1–S157.

Cremaschi L, von Versen, R, Benzing T, Wiesener M, Zink N, Milkovich N, Paivanas T, Gallagher M, Thaiss F, 'Induction therapy with rabbit antithymocyte globulin versus basiliximab after kidney transplantation: A health economic analysis from a German perspective' *Accepted for publication in Transplant International*.



NICE
Sent by NICE Docs

Date 18/05/2017

Dear NICE

Re Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85) [ID456]

Many thanks for giving us the opportunity to comment on the appraisal consultation document.

Our only comment is around the proposed date of review. With ongoing changes to product availability and licenses as new products are approved, we feel that it would be more pertinent to consider for review after 2 years rather than waiting for 3 years before a formal review as stated in the document.

Yours sincerely



Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX

Return address

- Head Office** Ridings Point, Whistler Drive, Castleford, West Yorkshire WF10 5HX..... | Tel. +44 (0)1977 628 500 | Fax. +44 (0)1977 628 799
- Eastbourne** Brampton Road, Hampden Park, Eastbourne, East Sussex BN22 9AG..... | Tel. +44 (0)1323 501111 | Fax. +44 (0)1323 512812
- Harlow** Field House, Station Approach, Harlow, Essex, CM20 2FB..... | Tel. +44 (0)20 7540 7000 | Fax. +44 (0)870 532 3334

Registered Office Ridings Point, Whistler Drive, Castleford, West Yorkshire WF10 5HX

Registered in England No. 302461 | VAT Reg. No. G.B. 675 2172 28 | Medical Information Unit | Tel. +44 (0)20 7540 7000

British Kidney Patient Association



21st May 2017

Response to NICE TA85 ACD on use of immunosuppressive therapy for adult kidney transplant patients

The British Kidney Patient Association (BKPA) is a national charity which works to improve quality of life for kidney patients through advocacy, direct grants, educating and informing patients, counselling and funding patient-centred research, healthcare professionals and projects.

The BKPA was extremely concerned about the previously proposed multiple technology appraisal on immunosuppressant therapies, which recommended that just 3 drugs (basiliximab, immediate-release tacrolimus and mycophenolate mofetil) should be used to prevent rejection of a kidney transplant.

The appraisal did not take account the impact of the recommendations on patients who may be unable to tolerate the recommended drugs, thereby making up to 20% of transplants likely to fail. It also had the potential to affect second or subsequent transplants when access to the range of drugs might be even more important if problems had developed with the three drugs.

We note that the revised recommendations in 1.5 go some way to recognising this issue:

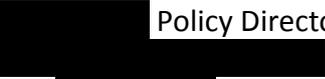
1.5 The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults who:

- are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or
- have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable for example, because of contraindications or intolerance.

We would like to thank the patient experts from our patient advisory group who attended the recent committee meeting. We hope that this revised guidance will allow sufficient flexibility for prescribing of currently commissioned immunosuppression agents (listed in 1.4) where clinical indications exist; we are encouraged that NICE accepted the points we made in our submissions to the appeal meeting in April 2016.

We note the reference to 'haemodialysis' three times on page 25 in the revised consultation document and request that this is amended to state '**dialysis**' as patients may **choose** to go onto either haemo or peritoneal dialysis and have the right to chose the therapy which suits them. The revised consultation makes it clear that both clinical and patient experts believe that a successful transplant offers the opportunity for an improved quality of life. We believe that the conclusions could be clearer on the costs in quality of life and side effects as well as costs to the system of the patient returning to dialysis if a transplant fails (dialysis is estimated at £30,800 pa not including transport costs, certain drugs, and the cost to carers <http://www.england.nhs.uk/wp-content/uploads/2014/04/a07-renal-transpl-ad-0414.pdf> and the costs of a failed transplant at £17,000).

Yours sincerely

 Policy Director
Tel: 



The Voice of Transplantation in the UK

22nd May 2017

Re: Appraisal Consultation Document (ACD): Immunosuppressive therapy for kidney transplant in adults, April 2017.

The British Transplantation Society (BTS) notes the ACD in response to the appeal process to the preliminary guidance (ID456) and welcomes the changes that have been made following the appeal hearing in March 2016. We endorse the response of our clinical expert and representative, Dr Nicholas Torpey, who has been closely involved throughout the process.

Specifically, we endorse:

The statements in section 4.20 of the guidance that clarify:

- The scope of the evidence and its application to immunosuppressive therapy given at the time of transplant
- The relevance of recommendations 1.1-1.4 to initial therapy only.
- That there are patients who will not tolerate the recommended therapy and that consideration of the management of these patients was beyond the scope of the original Assessment Group

We also endorse the proposal made by Dr Torpey about inclusion of a specific sentence to clarify the evidence to support ensuring that alternative, effective immunosuppressive therapy is made available to patients who are intolerant to calcineurin inhibitors (page 25). Such decisions are time-sensitive and appropriate funding mechanisms must be in place to facilitate effective changes in immunosuppressive therapy when individual patients require it.

In the interests of patient choice and to promote concordance, we support the inclusion of slow release tacrolimus in the recommendations if cost effective preparations can be sourced (3.12 and 4.13).

Thank you for the opportunity to comment on this consultation document.

Kind regards,

[Redacted]

[Redacted], On Behalf of the BTS

☎ 01625 664547

✉ secretariat@bts.org.uk

Registered Office: Chester House, 68 Chestergate, Macclesfield, Cheshire, SK11 6DY

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

RESPONSE TO ACD

From: [REDACTED] on behalf of The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group

As an independent group, the ESPRIT Group (www.esprit.org.uk) does not advocate any particular product and our opinions, recommendations and activities are all our own. As such we could not contribute to NICE's assessment of the *comparative* efficacy and cost-effectiveness of individual immunosuppressants included in the MTA. However, where the efficacy and safety of treatment of transplant patients is potentially threatened, we feel it of vital importance to highlight our concerns and the principles underlying them. This underpinned all the various arguments which we presented as part of the Appeal process following the last FAD.

Overall we were pleased with the provisions of this ACD and consider the latest recommendations to be sound and a suitable basis for guidance to the NHS. In particular we welcome:

- That the recommendations clearly only apply to the initial period of immunosuppression after transplantation
- It is reasonable that NICE is 'unable to make recommendations' for patients who are, or become, unable to have the recommended initial agents or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid. This reflects the importance of maintaining flexibility for experienced transplant professionals to provide tailored immunosuppression in line with the varying needs of individual transplant patients
- That it clearly states the recommendations are not intended to affect treatment with any technologies started in the NHS before the guidance is published - i.e. does not affect patients who are already being managed on clinically-tailored regimens - and clearly states that funding for these patient treatments should continue

We are in agreement with the proposal that the guidance gets reviewed again in three years.

Appraisal Consultation Document (ACD) – Immunosuppressive therapy for kidney transplant in adults – April 2017

Thank you for the opportunity to comment on this ACD. I have been involved in the evolution of this Multiple Technologies Assessment Guideline (MTAG) in several capacities, including:

- As a member of the British Transplant Society (BTS) Council – responding to earlier versions of this appraisal
- Representing the BTS, Renal Association and British Renal Society at the Appeal hearing in March 2016
- As a clinical expert at the Appraisal Group committee meeting in March 2017

I have read the current ACD (April 2017) carefully and the comments below are my own views as an invited clinical expert. I have also discussed the ACD with my colleagues at the BTS, shared my views, and contributed to the BTS response made separately.

Overall, I believe the current ACD fairly reflects the points that the committee were asked to address following the appeal hearing in March 2016. There are several key points:

1. Most importantly, there is now a clear statement that the evidence considered by the Assessment Group (AG) and used to inform this ACD is restricted to immunosuppression *given at the time of transplantation (both induction and maintenance treatment)* – section 4.20 - and that the recommendations summarized in points 1.1 – 1.4 apply only to such *initial treatment*.
2. Secondly, there is now a clear statement that a *significant cohort of patients will not tolerate the recommended initial treatment - section 4.20* - and that evidence regarding the management of immunosuppression in these patients was not considered by the AG nor forms part of this appraisal – reflected in recommendation 1.5 and in the last sentence of section 4.20.
3. Perhaps the key clinical issue is the management of patients intolerant of calcineurin inhibitors (tacrolimus and ciclosporin). At the committee meeting in March 2017 I drew attention to two recent clinical studies in which tacrolimus was deliberately withdrawn from an immunosuppressive regimen almost identical to that recommended in this ACD. Both trials were terminated early by data monitoring committees because of an unacceptable rate of rejection following tacrolimus withdrawal^{1,2}. These reports emphasize the need for alternative immunosuppressive options for those patients unable to continue with calcineurin inhibitors. Would it be useful to include a comment such as *'a clinical expert drew attention to recent trials emphasizing the requirement for effective alternative immunosuppression in those patients intolerant of calcineurin inhibitors'* in addition to the sentence beginning on line 10, page 25

4. Section 4.20 is quite long. Would it be reasonable to split it into 2 parts at the point identified above (line 12, page 25)? I think it would be useful in the second section – which is a helpful discussion on the alternatives to calcineurin inhibitors – to clarify the point that there is a significant and recognizable *cohort* of patients for whom alternatives to calcineurin inhibitors may be required. Accordingly the current NHSE system for Individual Funding Requests (IFR) that requires ‘exceptionality’ is *clearly* inappropriate. The final sentence (page 26, lines 5-9) is critically important, emphasizing recommendation 1.5.
5. Section 1.2 refers specifically to Modigraf (tacrolimus granules), indicating that Modigraf may be used if available at an agreed cost. My recollection from the appeal hearing is that, after some discussion, there was acknowledgement that prolonged release tacrolimus (Advagraf) was equally effective as twice daily preparations, but more expensive (sections 3.12 and 4.13). Would it be reasonable to add a statement indicating that prolonged release tacrolimus is an acceptable alternative to standard release preparations if available at equivalent cost?

References

1. Dugast E, Soulillou J-P, Foucher Y et al (2016). Failure of calcineurin inhibitor (tacrolimus) weaning randomized trial in long-term stable kidney transplant recipients. *Am J Transplant* **16**: 3255-3261.
2. Hricik D, Formica R, Nickerson P et al (2015). Adverse outcomes of tacrolimus withdrawal in immune-quiescent kidney transplant recipients. *J Am Soc Nephrol* **26**: 3114-3122.

Comments on the ACD Received from the Public through the NICE Website

Name	[REDACTED]
Role	NHS Professional
Other role	Consultant nephrologist and transplant physician
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
General	rATG has been acknowledged to be clinically effective as are many other immunosuppressants that are part of this review namely, prolonged release tacrolimus and belatacept. What the review does not adequately capture or account for is increased risk of graft loss due to non-adherence leading morbidity and increased mortality associated with return to dialysis. Every clinical decision even though not cost effective is made based on the risk and balance of mortality on dialysis versus prolonging transplant graft function. Belatacept is likely to be cost effective if the reduced incidence of MI, CVA and drugs used to treat hyperlipidemia, NODAT, increased hospital visits due to these complications are all taken in to account.
Date	19 May 2017

ID456 Immunosuppressive therapy for kidney transplant in adults

AG comments on ACD consultation responses

1. Argument: Wording of 1.5 appears to suggest rATG not recommended to treat steroid-resistant acute rejection

Response: Have not read 1.5 so can't comment on whether this is a fair reading, but it is not something we produced any evidence for and we are not aware of any Committee discussions on this point and agree it is outside the scope of the appraisal.

2. Argument: More to risk than just PRA and PRA > 0% considered high risk anyway

Response: Not really sure on this point. Yes it's undoubtedly reasonable to say PRA isn't the whole story, but NICE is particularly interested in PRA and 80% threshold because of basiliximab marketing authorisation. If PRA > 0% is high risk, do other studies we included besides Brennan 2006 also count as "high risk" studies? They want separate recommendations for the "high risk" population (can't work out if they want basiliximab excluded as a comparator in this or not) and want Brennan 2006 to be the only study considered. Not sure if they have a point or not.

3. Argument: Model didn't include antibody-treated acute rejection, which was higher for basiliximab than rATG in Brennan 2006

Response: Agree the model does not differentiate by severity of rejection, and antibody-treated acute rejection would be more expensive than acute rejection which resolves with steroid treatment. Agree that Brennan 2006 found higher rates of antibody-treated acute rejection in basiliximab arm and this was statistically significant, although note that it is an open-label study.

4. Argument: Cost of failure £3,557 used in the model is from unpublished study and is an underestimate

Response: This refers to average cost of acute rejection, not to graft failure. As an independent assessment group we believed that the study supplied by one of the companies involved in the appraisal was the best available evidence, but it was supplied in confidence.

5. Argument: Grafts at high risk are likely to receive similar rates of prophylaxis regardless of therapy

Response: We accept that we did not conduct a review of current practice and note that a clinical expert (Prof C Watson) in his response to the Assessment Report stated that "prophylaxis and monitoring of CMV is very variable and may differ where rATG is used routinely". The model we produced assumed no difference in the rate of CMV infection, but did assume more use of prophylaxis in the rATG arms. We agree that the model will produce more favourable cost-effectiveness estimates if equal prophylaxis is used in the rATG arms and the rates of CMV infection are maintained equal across the induction therapies. The model currently estimates an average increase in prophylaxis costs of £926 for the rATG arms. Removing this additional cost (in isolation)

does not lead to rATG becoming cost-effective in the deterministic base case (still dominated by basiliximab), although this is not focussed on a high-risk group.

6. Argument: Taken altogether, the changes in rates of events and costs mean that the ICERs for rATG have been overestimated

Response: We believe that Sanofi have received a copy of the economic model produced by the assessment group. If Sanofi have the version with a sheet titled "Corrections" we invite them to make any changes they feel are justifiable and to report the resulting cost-effectiveness results.