rabbit anti-human thymocyte immunoglobulin, 25mg powder for
solution for infusion (Thymoglobuline®)                             No. (489/08)
Genzyme Therapeutics Ltd

04 July 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above
product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on
its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rabbit anti-human thymocyte immunoglobulin, 25mg powder for solution for infusion
(Thymoglobuline®) is not recommended for use within NHS Scotland for prevention of graft
rejection in renal transplantation.

Compared with an alternative agent for induction of immunosuppression it was associated
with a lower rate of acute rejection but this did not translate into improved patient or graft
survival within the 12-month study period. The manufacturer has not presented a sufficiently
robust economic analysis to gain acceptance by SMC.

Rabbit anti-human thymocyte immunoglobulin is also licensed for the treatment of steroid
resistant graft rejection in renal transplantation and for the prevention of graft rejection in
heart transplantation. The manufacturer’s submission related only to the prevention of graft
rejection in renal transplantation. SMC cannot recommend the use of rabbit anti-human
thymocyte immunoglobulin for these additional indications.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
Indication
Immunosuppression in solid organ transplantation
- Prevention of graft rejection in renal transplantation
- Treatment of steroid-resistant graft rejection in renal transplantation
- Prevention of graft rejection in heart transplantation

Dosing information
For prophylaxis of acute graft rejection, 1 to 1.5mg/kg/day for 3 to 9 days after transplantation of a kidney, corresponding to a cumulative dose of 3 to 13.5 mg/kg.

Product availability date
April 2008

Summary of evidence on comparative efficacy
Rabbit anti-human thymocyte immunoglobulin (rabbit ATG) is a selective immunosuppressive agent, mostly acting on T-lymphocytes, and this submission considers its use as induction therapy in prevention of graft rejection in renal transplantation.

Two further indications, treatment of steroid-resistant graft rejection in renal transplantation and prevention of graft rejection in heart transplantation, are not considered in this submission.

One phase II open-label prospective randomised efficacy study compared induction therapy with rabbit ATG or basiliximab in patients who received a solitary renal allograft from a deceased donor and were at high risk for acute rejection or delayed graft function. The high risk category included all patients who received a transplant from a non-heart beating donor or with > 24 hours cold ischaemia time (>30 hours with machine perfusion). Other patients were required to meet additional donor and/or recipient criteria for high risk. Patients (n=278) were assigned to receive either rabbit ATG or basiliximab according to 1:1 variable-block randomisation.

Rabbit ATG 1.5mg/kg was given intraoperatively and continued for up to 4 days (doses could be reduced or withheld if the neutrophil and/or platelet counts fell below defined limits), and basiliximab 20mg was given intraoperatively and on postoperative day 4. All patients also received maintenance therapy with mycophenolate mofetil (MMF), methylprednisolone starting on the day of the transplant then oral prednisone taper and ciclosporin initiated when adequate renal function was established or on postoperative day 4 if not before then.

The primary endpoint was a composite of biopsy-confirmed acute rejection (BCAR), delayed graft function, graft loss and death. Delayed graft function was defined as the need for dialysis within seven days of transplant. The individual components of the primary endpoint were also studied. At 6 and 12 months there was no significant difference between groups receiving rabbit ATG and basiliximab for the composite endpoint. The rate of BCAR at 12 months was significantly lower in the rabbit ATG group compared to basiliximab and the rate of severe BCAR defined as requiring antibody therapy (also known as steroid resistant acute rejection) was also significantly lower however there was no significant difference for delayed graft function, graft loss or death.
Event rates at 12 months from a Phase II trial comparing rabbit anti-human thymocyte immunoglobulin and basiliximab as induction therapy for renal transplantation in high-risk patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rabbit anti-human thymocyte immunoglobulin (N=141) (n %)</th>
<th>Basiliximab (N=137) (n %)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>71 (50%)</td>
<td>77 (56%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Biopsy-proven acute rejection (BCAR)</td>
<td>22 (16%)</td>
<td>35 (26%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Antibody-treated acute rejection</td>
<td>2 (1.4%)</td>
<td>11 (8.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>57 (40%)</td>
<td>61 (44%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Graft loss</td>
<td>13 (9.2%)</td>
<td>14 (10%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Death</td>
<td>6 (4.3%)</td>
<td>6 (4.4%)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

* Composite of BCAR, delayed graft function, graft loss or death

Further evidence comparing rabbit ATG and basiliximab comes from two safety studies and one retrospective observational study with varying risk criteria for entry into the trials. None of these recorded a significant difference between treatment groups for delayed graft function, graft loss or death, and rabbit ATG was associated with a significantly reduced incidence of acute graft rejection only in the observational study.

Summary of evidence on comparative safety

In one open-label randomised safety study, 103 patients scheduled to undergo a first cadaveric renal transplant were randomly assigned on a 1:1 basis to receive either basiliximab (20mg given within 2 hours prior to transplantation and on postoperative day 4) or rabbit ATG (1-1.5mg/kg within 24 hours of transplantation then adjusted according to CD2+ or CD3+ counts. In the safety population (n=101, rabbit ATG n=50; basiliximab n=51) the incidence of treatment-related adverse events was significantly higher with rabbit ATG than basiliximab (48% versus 16%) as was the incidence of fever (32% versus 2.0%), infections (86% versus 65%) and cytomegalovirus (CMV) infection (38% versus 12%).

In the second open-label randomised safety study, 107 patients were randomised to receive either basiliximab (20mg within 2 hours prior to transplantation and postoperative day 4) or rabbit ATG (1mg/kg intraoperatively and postoperative day 1 and then adjusted to CD3+ counts). The safety population consisted of 105 patients (rabbit ATG n=53; basiliximab n=52). The primary objective was to compare the proportion of patients experiencing treatment-related adverse events with particular reference to those associated with immunosuppression. There was no significant difference between groups for fever, serum sickness or infections. However rabbit ATG was associated with a significantly higher incidence of CMV infection (42% versus 21%), leukopenia (51% versus 19%) and thrombocytopenia (30% versus 0%).

In the efficacy study the overall incidence of adverse events and serious adverse events was similar between groups but rabbit ATG was associated with a significantly higher incidence of infections and infestations (77%, 100/141 versus 61%, 84/137), blood and lymphatic system (75% versus 57%) and skin and subcutaneous tissue disorders (36% versus 24%). The higher rate of infection was mainly due to urinary tract infections, and the incidence of CMV infection was significantly lower in the rabbit ATG group in this study (7.8% versus 18%). The basiliximab group had significantly more immune system disorders (23% versus 13%).
Summary of clinical effectiveness issues

Despite 6-month analysis indicating that 340 patients should be enrolled into the pivotal trial, recruitment to the study was discontinued after enrolment of 278 patients due to the statistical improbability of a change in the primary endpoint with further enrolments. In addition, although the study design was amended to include 4 years follow-up after the main study period, follow-up was discontinued because of concerns about data management in this phase of the trial.

Thus data are lacking for the effectiveness of rabbit ATG beyond 12 months post-transplantation and information on long term outcomes is limited, as are data on the effect on quality of life. Episodes of acute rejection are a risk factor for chronic rejection and graft loss, however the reductions in the rate of BCAR with rabbit ATG compared with basiliximab did not translate into significant reduction in delayed graft function, graft loss or death in any of the studies included in this submission: the pivotal trial did not show a statistically significant improvement in delayed graft function or in graft or patient survival.

Infection with CMV virus was significantly more common with rabbit ATG in both safety studies and with basiliximab in the efficacy study. The incidences varied between studies, possibly reflecting differences in CMV prophylaxis medication. Prophylaxis was recommended for all recipients in the efficacy study who were seropositive for CMV and/or received a transplant from a seropositive donor; for no patients in the first safety study and only for seronegative patients receiving a graft from a seropositive donor in the second.

In the efficacy study, where the overall rate of infections and infestations was significantly more common with rabbit ATG, antibiotic prophylaxis (as distinct from CMV prophylaxis) was also significantly lower in this group (19% versus 31%).

A NICE appraisal which reviewed immunosuppressive therapy for renal transplantation concluded that, although basiliximab and daclizumab are not licensed for patients who are at high immunological risk, they should be options for all adults undergoing renal transplantation, irrespective of their immunological risk. It states that induction therapy with alternative agents, including ATG, has been used extensively in the USA but use has been more limited in the UK where the agents' side effects are considered unacceptable. The advice does not specify which ATG products were considered or the conditions under which induction therapy was used.

NICE also presented pooled analysis of data for basiliximab, the active comparator for trials with rabbit ATG, and found no significant differences in patient survival, graft loss or rates of BACR compared with other induction agents. A pooled analysis of data from placebo-controlled trials also found no significant differences in patient or graft survival rates, however basiliximab was associated with a significantly lower incidence of BACR.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing treatment with rabbit ATG to basiliximab for the induction of immunosuppression in patients considered to be at increased risk of acute graft rejection in renal transplantation. A decision tree was used for the first year of the model and was based on data from the pivotal clinical trial. Subsequent years were modelled based on data from a follow-up study of the pivotal trial and additional data from UK Transplant and UK Renal Registry. The manufacturer estimated that treatment with
rabbit ATG was dominant i.e. it was less costly and more effective than basiliximab, with estimated savings of £4,175 and a QALY gain of 0.05.

Basiliximab appears to be an appropriate comparator as clinical experts indicated that it was the predominant treatment in Scotland. The utility values used were generally appropriate and the sensitivity analysis showing the effect of removing non-significant outcomes from the analysis was helpful. No indirect comparison was required as comparative trial data were available. However there were some concerns with the pivotal trial, including the failure of the primary composite endpoint to reach statistical significance. Key drivers of the results were improvements in graft survival and patient survival in patients treated with rabbit ATG compared to basiliximab. However, these estimates were extrapolated from acute rejection data rather than being based on outcomes seen in clinical studies, and this represents a weakness in the analysis.

Initially, no quality of life loss due to adverse events was incorporated into the analysis. SMC clinical experts commented that rabbit ATG has a more serious adverse event profile than the other treatments currently used for these patients. Additional sensitivity analysis was provided by the company to show the impact of adverse events on patients’ quality of life. However, it only showed the effect of assuming a disutility for a period of two weeks for each adverse event individually and this may not adequately have captured the adverse event profile from the trial.

In summary, due to the concerns about weaknesses in the clinical evidence base which underpins the economic model, the lack of appropriate sensitivity analysis to show the effect of all adverse events on patients’ quality of life and the lack of data from the follow-up study to enable appropriate assessment of the model results, the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

### Summary of patient and public involvement

A Patient Interest Group Submission was not made.

### Additional information: guidelines and protocols

NICE Technology appraisal 85, reviewing immunosuppressant therapy in renal transplantation, is discussed in the clinical effectiveness section.

### Additional information: comparators

Patients undergoing renal transplantation require long-term immunosuppressant therapy but induction therapy is given to some patients for about two weeks immediately postoperatively with the aim of ‘switching off’ the immune system to reduce the likelihood of acute rejection and delay initiation of nephrotoxic calcineurin inhibitors. The term induction therapy has been linked to the polyclonal antibodies antithymocyte immunoglobulin (ATG) and anti-lymphocyte antibody (ALG), the monoclonal antibody muromonab-CD3 and basiliximab or daclizumab - monoclonal antibodies with specificity for CD25. Licensed options are included in the table below.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit anti-human thymocyte immunoglobulin</td>
<td>1.0 to 1.5 mg/kg/day by IV infusion for three to nine days</td>
<td>1513 to 6054</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>1mg/kg by IV infusion for a total of five doses</td>
<td>3355</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>20 mg IV injection or infusion for two doses</td>
<td>1685</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. IV = intravenous.
Doses are based on a 70kg individual, rounded to the nearest vial size.
Costs from Monthly Index of Medical Specialities, April 2008 except for rabbit anti-human thymocyte immunoglobulin, provided by the manufacturer on 31st March.

Additional information: budget impact

The manufacturer estimated net savings of £15k in year 1 and £292k in year 5. These savings include the cost of BCAR, dialysis costs and costs associated with adverse events. The net drug budget impact was estimated to be £10k in year 1 rising to £97k in year 5. These figures are based on 7 patients receiving rabbit ATG in year 1 rising to 67 in year 5. The predicted market share was 10% in year 1 rising to 100% by year 5. 100% market share may be an overestimate as experts have indicated that rabbit ATG would only be used in a minority of cases.
Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 June 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.


