Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Angela Timoney FRPharmS
NHS SCOTLAND

belatacept powder for concentrate for solution for infusion 250mg vial and disposable syringe (Nulojix®) SMC No. (786/12)

Bristol Myers Squibb Pharmaceuticals Ltd

04 May 2012

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

ADVICE: following a full submission

belatacept (Nulojix®) is not recommended for use within NHS Scotland.

Indication under review: Belatacept, in combination with corticosteroids and a mycophenolic acid, is indicated for prophylaxis of graft rejection in adults receiving a renal transplant. It is recommended to add an interleukin-2 receptor antagonist for induction therapy to this belatacept-based regimen.

Results of two phase III studies have demonstrated comparable graft and patient survival of belatacept versus a calcineurin inhibitor when used as part of a maintenance immunosuppressive regimen. Indirect efficacy data from a mixed treatment comparison are available for belatacept versus another calcineurin inhibitor, considered the key comparator in NHS Scotland.

The submitting company's justification for the treatment's cost in relation to its health benefits was not sufficient and in addition, the company did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Belatacept, in combination with corticosteroids and a mycophenolic acid, is indicated for prophylaxis of graft rejection in adults receiving a renal transplant. It is recommended to add an interleukin-2 receptor antagonist for induction therapy to this belatacept-based regimen.

Dosing Information

Initial phase: belatacept 10mg/kg as an intravenous (iv) infusion at a constant rate over 30 minutes on the day of transplantation (day 1) prior to implantation, and then on day 5, day 14, day 28, end of week 8, end of week 12.

Maintenance phase: starting at end of week 16, belatacept 5mg/kg iv every 4 weeks.

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of renal transplant patients.

Product availability date

5 September 2011

Summary of evidence on comparative efficacy

Belatacept belongs to a new class of immunosuppressive agents that targets the blockade of CD28:CD80/CD86 interactions, one of two key co-stimulatory signals required for T cell activation. Activated T cells are the most important immune mediators of allograft rejection. Belatacept is administered as a 30 minute intravenous (iv) infusion and, following the initial treatment phase, a dose of 5mg/kg iv is administered every 4 weeks.

Two similarly designed, phase III, randomised, partially-blinded, multi-centre studies were conducted in adult patients and compared two iv belatacept regimens (more intensive [MI] and less intensive [LI]) with oral ciclosporin.[1,2] The BENEFIT study[1] was conducted in patients receiving a graft from a standard criteria donor, a living donor or deceased donor with anticipated cold ischaemic time <24 hours, and the BENEFIT-EXT study[2] in patients receiving a graft from an extended criteria donor (ECD). An ECD was defined as donor age ≥60 years; or donor age ≥50 years and ≥2 risk factors (cerebrovascular accident, hypertension, serum creatinine ≥1.5mg/dL); or an anticipated cold ischaemic time ≥24 hours; or donor with cardiac death.

Patients were randomised equally (and stratified by study site) to belatacept MI regimen, belatacept LI regimen (licensed dose regimen) or ciclosporin twice daily (to achieve a serum concentration of 150 to 300 nanograms/mL during the first month and thereafter a target level of 100 to 250 nanograms/mL). The belatacept MI regimen used a higher dose of belatacept than the licensed regimen and is not discussed further. The belatacept LI regimen consisted of 10mg/kg on days 1 and 5, then at weeks 2 and 4, then every 4 weeks to end of month 3, then 5mg/kg every 4 weeks thereafter. All patients received induction with basiliximab 20mg iv on days 1 and 5, and a maintenance regimen of mycophenolate mofetil 1g orally twice daily and methylprednisolone 500mg iv on day 1,250mg iv on day 2 and orally thereafter tapered to a

dose of ≥2.5mg/day. In addition, antiviral prophylaxis was recommended for at least 3 months post-transplant and for 3 months from the initiation of T-cell depleting agent (which was permitted in patients in the ciclosporin group for anticipated delayed graft function and for the treatment of rejection in all groups). Prophylaxis against pneumocystis was also recommended for 6 months.

The co-primary outcomes were assessed at 12 months and were a composite of patient and graft survival, renal impairment and, in the BENEFIT study only, the incidence of acute rejection (defined as histologically confirmed rejection as determined by the central pathologist). For the patient and graft survival endpoint graft loss, cause of graft loss and death were adjudicated by committees blinded to study treatment. The composite renal impairment outcome was defined as patients with a glomerular filtration rate (GFR) <60mL/min/1.73m^2 at month 12 or a decrease in measured GFR ≥10mL/min from month 3 to 12. In both studies, analyses were performed on the intention to treat population defined as randomised patients who received a transplant. A sequential testing procedure was used with the following hierarchy: firstly, patient and graft survival at 12 months (10% non-inferiority margin); secondly, composite renal endpoint at 12 months (superiority); thirdly (in BENEFIT study only), acute rejection at 12 months (20% non-inferiority margin); and lastly, chronic allograft nephropathy (secondary endpoint) at 12 months (superiority).

Belatacept was non-inferior to ciclosporin for patient and graft survival. In the BENEFIT study, significantly fewer patients treated with belatacept than ciclosporin met the renal impairment endpoint. Belatacept was non-inferior (using a 20% margin) to ciclosporin for acute rejection in both studies (primary endpoint for BENEFIT study only). Results of the co-primary endpoints are included in the table below.

Table: co-primary endpoints at month 12 for BENEFIT and BENEFIT-EXT studies for belatacept LI and ciclosporin.

Endpoint	**BENEFIT**		**BENEFIT-EXT**	
	Belatacept LI	**Ciclosporin**	**Belatacept LI**	**Ciclosporin**
n	226	221	175	184
Patient and graft survival; n (%)	218 (97%)	206 (93%)	155 (89%)	156 (85%)
Difference (97.3% CI)	3.2% (-1.5 to 8.4)	-	3.8% (-4.3 to 11.9)	-
Renal impairment;				
number of patients included in analysis [5,6]	214	213	169	178
n (%)	116 (54%)	166 (78%)	130 (77%)	151 (85%)
Difference (97.3% CI)	-23.7% (-33.3 to -13.7)	-	-8.4%, (-17.8 to 1.0)	-
Acute Rejection*; n (%)	39 (17%)	16 (7.2%)	31 (18%)	26 (14%)
Difference (97.3% CI)	10.0% (3.3 to 17.1)	-	3.6% (-5.0 to 12.3)	-

LI=less intensive, CI=confidence interval. * Secondary endpoint for the BENEFIT-EXT study.

Chronic allograft nephropathy was numerically more prevalent in ciclosporin than belatacept LI treated patients in BENEFIT and similar between groups in BENEFIT-EXT. The mean

measured GFR, another secondary endpoint, was 63.4mL/min/1.73m^2 for belatacept LI and 50.4mL/min/1.73m^2 for ciclosporin in BENEFIT, and 49.5mL/min/1.73m^2 and 45.2mL/min/1.73m^2 respectively in BENEFIT-EXT. The incidence of new-onset diabetes after transplant (NODAT) was defined as a requirement for anti-diabetic medication for ≥30 days, or ≥2 days fasting plasma glucose tests ≥126mg/dL. The incidence of NODAT was numerically lower for belatacept (4% to 5%) than ciclosporin (9% to 10%) in both studies.

In both studies by month 12, patients had returned to physical and mental health functioning levels comparable to the general population with respect to all Short Form (SF)-36 scores, irrespective of the treatment regimen.

At 36 months, the proportion of patients surviving with a functioning graft in BENEFIT study was 92% versus 89% in the belatacept LI and ciclosporin groups respectively (difference 3.3%, 97.3% CI: -2.9 to 9.8), and in BENEFIT-EXT 82% versus 80% (difference 2.4%, 97.3% CI:-6.9 to 11.6).[3] In BENEFIT, there were no additional cases of acute rejection in years 2 and 3 in the belatacept LI group and five cases in the ciclosporin group.[4]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In general, the most common adverse events (anaemia, constipation, diarrhoea and nausea) occurred in similar proportions of patients in both studies. In BENEFIT, serious adverse events occurred in 44% (100/226) versus 57% (126/221) of patients in the belatacept LI and ciclosporin groups respectively. In BENEFIT-EXT, the incidence of serious adverse events was similar between groups.

In data up to two years, post transplant lymphoproliferative disorder occurred in a total of 12 patients in the phase III studies: five patients on belatacept MI, six patients on belatacept LI and one patient on ciclosporin.[1,2,5] The risk is higher in patients who are Epstein-Barr virus (EBV) seronegative and therefore EBV serology should be ascertained before starting administration of belatacept. Belatacept is contraindicated in transplant recipients who are EBV seronegative or with unknown serostatus. At 2 years post-transplant in BENEFIT, there were seven deaths on belatacept MI, nine on belatacept LI and 14 on ciclosporin respectively, and in BENEFIT-EXT, 19, 13 and 16 deaths respectively.[5] In both studies, the most common cause of death was infection.

In BENEFIT-EXT, graft thrombosis occurred more frequently in the belatacept groups (4.3% and 5.1% for the MI and LI regimens respectively), than in the ciclosporin group (2.2%).

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Two large randomised phase III studies provide evidence of comparative efficacy of belatacept versus ciclosporin in patients receiving a graft from a standard or extended criteria donor. At 12 months, the non-inferiority of the belatacept licensed dose regimen over ciclosporin was shown for the composite endpoint of patient and graft survival in both studies. However, for the

composite renal impairment endpoint, there was a significant difference in favour of belatacept in the BENEFIT study only. The higher calculated GFR in belatacept compared to ciclosporin treated patients in both studies is considered to be a clinically meaningful effect.[3] Belatacept was non-inferior (using a 20% margin) to ciclosporin for acute rejection in both studies and there were few additional cases of acute rejection beyond 12 months.

Efficacy data are available up to 3 years when the proportion of patients surviving with a functioning graft was 82% to 92% in patients treated with the recommended dose of belatacept compared to 80% to 89% for ciclosporin. Results at 12 and 24 months were sustained to 36 months.

In BENEFIT, the mean age of recipients and donors was low and nearly 60% of grafts were from living donors suggesting low risk. The European Medicines Agency considered the BENEFIT-EXT population was more relevant for European renal transplant recipients.[3]

Tacrolimus is the most relevant comparator according to clinical experts consulted by SMC, but no direct comparative efficacy data were identified. The submitting company included a network meta-analysis (NMA) which included 32 studies of tacrolimus versus ciclosporin or belatacept versus ciclosporin. The NMA has limitations in terms of heterogeneity. Results were presented for a number of outcomes at 12 and 36 months and demonstrated that belatacept and tacrolimus are similar in terms of graft loss. Expert statistical advice sought by SMC considered that the indirect comparison was a fairly extensive and thorough NMA.

The introduction of belatacept would require a 30 minute iv infusion every 4 weeks on a long-term basis. This would have implications for the patient and for service delivery as patients would otherwise be receiving oral immunosuppressive regimens. Infusion-related reactions occurred in approximately 5% of patients up to year 3; most events were not serious, were mild to moderate in intensity, and did not recur. The use of ciclosporin and tacrolimus requires therapeutic drug monitoring to determine the optimal dose. No such monitoring is required for belatacept. Experts consulted by SMC considered the potential for reduced nephrotoxicity of belatacept versus calcineurin inhibitors (such as ciclosporin and tacrolimus) to be an important theoretical advantage.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing belatacept with both ciclosporin and tacrolimus as prophylaxis treatment of graft rejection in adults receiving a renal transplant. A model was used which was structured in the form of a decision tree for the trial period (up to 3 years post-transplant) followed by a Markov model to estimate the longer-term outcomes following transplant and initial follow-up. The time horizon was 40 years with patients starting the model aged 43 years. Sensitivity analyses using both longer and shorter time horizons were also provided. The model consisted of the following health states: functioning graft where patients were classified from GFR stage 2 to GFR stage 4, graft failure (GFR stage 5 where patients are on dialysis), re-transplantation and death. The model also accounted for patients experiencing acute rejection episodes, new onset diabetes after transplantation and post-transplant lymphoproliferative disorder.

The clinical data used in the initial decision tree phase of the model were taken from the two pivotal studies comparing belatacept with ciclosporin. A NMA was conducted comparing belatacept with tacrolimus. The results showed that mean GFR was numerically (but not significantly) higher for belatacept than tacrolimus. The distribution of patients by GFR stage formed the basis of the extrapolation phase of the model. The mean calculated GFR was taken from the pooled studies for the belatacept and ciclosporin arms, and from the NMA for the tacrolimus arm. It was then assumed that the proportion of patients in each GFR stage could be estimated by assuming a normal distribution. Based on these assumptions around 41% of patients in the belatacept arm were assumed to be in the better GFR health state (stage 2) compared with 25% in the tacrolimus arm and 18% in ciclosporin arm. The company used existing risk equations from the US renal data system (USRDS) data to estimate transition probabilities for patients moving from each GFR stage to the other health states in the model in the extrapolation phase. It is therefore assumed that the patient characteristics of the USRDS dataset are comparable to Scottish patients. In addition, the model applies a hazard ratio of 0.85 to the survival equations in the belatacept arm to account for reduced nephrotoxicity associated with belatacept.

The utility values were derived from a study of post-transplant patients at the Renal Unit at the University Health Board Cardiff. The aim of the study was to explore the relationship between renal function after transplantation (as measured by GFR) and quality of life. Patients were asked to complete an EQ-5D questionnaire and UK tariff scores were then applied to the outputs from the EQ-5D survey to derive utility values. Disease management costs, such as routine outpatient attendances, lab tests, monitoring costs, hospitalisation and the management of renal related post-transplant events have been included based on GFR stage. The resource use estimates were based on a retrospective observational study conducted for the company using information from the Cardiff Renal Transplant Database.

For the comparison with ciclosporin, the company estimated a base case cost per quality adjusted life year (QALY) of £22,551 based on an incremental cost of £44,173 and a QALY gain of 1.96. For the comparison with tacrolimus the company estimated a base case cost per QALY of £49,977 based on an incremental cost of £85,602 and a QALY gain of 1.71. SMC experts have confirmed that tacrolimus is the main comparator.

There are a number of weaknesses with the analysis:

- Some of the clinical data used in the model from both the direct studies and the NMA were based on non-significant differences. When the non-significant differences were removed the incremental cost-effectiveness ratios (ICER) increased to £33K vs ciclosporin and £103K vs tacrolimus.
- The BENEFIT-EXT population is likely to be more representative of patients in practice. The company was unable to provide the results of the NMA based only on ECD patients as none of the tacrolimus studies reported the results for ECD patients separately. Therefore, the results of the economic analysis may not be generalisable to Scottish patients.
- The method used to estimate the distribution of patients across the GFR stages involved a number of assumptions. The NMA showed that the difference in mean calculated GFR at 36 months was not statistically significant for the comparison with tacrolimus. Therefore, it may not be appropriate to assume there are more patients in the better GFR stages in the belatacept arm. In addition, the assumption that patients can be classified by GFR based on a normal distribution may not be appropriate.

- Applying a hazard ratio of 0.85 to graft loss and mortality in the belatacept arm may double count the reduction in nephrotoxicity associated with belatacept treatment. It could be argued that this benefit is already captured in the distribution of patients by GFR stage at the start of the extrapolation period as there are more patients in the belatacept arm in the better health states. The basis of the 0.85 figure is also unclear. When a hazard ratio of 1 was used, the ICERs increased to £28K and £62K per QALY for the comparisons with ciclosporin and tacrolimus respectively.
- The utility values used in the model may be too low. For example, while it is recognised that patients on dialysis can have a relatively low quality of life, the utility value of 0.28 used for this health state appears particularly low. The company argued that the utility value was based specifically on dialysis patients post-transplant and therefore cannot be compared to dialysis related utility values in general. While it may be expected that patients would have a low quality of life immediately following transplant, the committee felt that it was unlikely that patients' quality of life would remain at this level. In addition, there was a general concern about the quality of the utility study as it is unpublished and based on relatively small patient numbers.
- There was some uncertainty associated with the costs of tacrolimus as these could not be reproduced accurately.
- The base case cost per QALY in the comparison with tacrolimus is above acceptable thresholds and is likely to be higher.

The significant weaknesses outlined above indicate the base case analysis is likely to underestimate the cost per QALY of belatacept. Therefore the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was received from: National Kidney Federation.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence published technology appraisal 85, Immunosuppressive therapy for renal transplantation in adults, in September 2004. The guidance includes the following recommendations [relevant to current submission];

- Tacrolimus is an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen in renal transplantation for adults. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for individual people.

The UK Renal Association issued Post-operative care of the kidney transplant recipient guidelines in February 2011. The following recommendations are made;

- Maintenance immunosuppression should normally consist of a calcineurin inhibitor (CNI) and an anti-proliferative agent, with or without corticosteroids in low and medium immunological risk kidney transplant recipients.

- Low dose tacrolimus (trough target 3 to 7 nanograms/mL) is recommended as the CNI of choice in patients also taking steroids who are low and medium immunological risk and are not at high risk of developing NODAT.
- Aim for minimum target levels for CNIs in uncomplicated renal transplantation after 3 months.
- For maintenance immunosuppression CNIs should be continued rather than withdrawn.

The guidance includes the following strategies in high risk patients with non-adherence; education or a simplified regimen of alemtuzumab or belatacept.

Additional information: comparators

Tacrolimus or ciclosporin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Belatacept	Intravenous infusion, 10mg/kg on days 1 and 5, then at week 2, 4, 8 and 12 then 5mg/kg every four weeks	13,472 in year 1, then 9,218 per year thereafter
Tacrolimus (Prograf®)	Orally, 1mg to 4mg twice daily	1,169 to 4,675
Tacrolimus prolonged release (Advagraf®)	Orally, 2mg to 8mg once daily	1,042 to 3,507
Ciclosporin	Orally, maintenance dose; 2 to 6mg/kg/day as two divided doses	941 to 2,582

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29 February 2012. Costs based on body weight of 70kg. Costs do not include induction regimen (but does include the belatacept initial phase), additional maintenance drugs and antiviral prophylaxis. The dose range for tacrolimus is based on the licensed dose, the dose used in a clinical study[6] and SMC clinical expert feedback. Generic preparations of tacrolimus (normal and prolonged release) are available; costs for branded formulations have been included in the cost table as they reflect use in NHS Scotland.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 175 patients in year 1 rising to 877 in year 5. The company assumed 20% of eligible patients would be treated with belatacept on the basis that only higher risk patients would be treated. This resulted in 35 patients in year 1 and 175 in year 5. The impact on the medicines budget was estimated at £433K in year 1 and £2.16m in year 5. The net medicines budget impact was estimated at £417K in year 1 and £2.08m in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). Am J Transplant 2010; 10: 535-46
2. Durrbach A, Pestana JM, Pearson, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant 2010; 10: 547-57
3. European Medicines Agency. Assessment report Nulojix (belatacept). EMEA/H/C/2098. www.ema.europa.eu
4. Vincenti F, Larsen CP, Alberu J et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant 2011 doi:10.1111/j.1600-6143.2011.03785.x
5. Larsen CP, Grinyo J, Medina-Pestana J, et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. Transplantation 2010; 90 (12): 1528-35
6. Eckberg H, Tedesco-Silva H, Demirbas A et al. Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation New England Journal of Medicine. 2007;357:2562-75.

This assessment is based on data submitted by the applicant company up to and including 13 April 2012.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.