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ABCIXIMAB (Reopro[®])

A Critical Assessment of the NSW Therapeutic Assessment Group Inc.

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EXECUTIVE SUMMARY

Clinical Summary

Abciximab is a mouse-derived monoclonal antibody targeted against glycoprotein IIb/IIIa on platelets resulting in platelet inhibition. Abciximab is used as an adjunct along with aspirin and heparin in Percutaneous Transluminal Coronary Angioplasty (PTCA). The recommended therapy is a bolus injection of 0.25mg/kg followed by a continuous infusion of 10mcg/min for 12 hours.

The submission was generally well presented and based on the companies submission to the PBAC for PBS listing. A major drawback, however, was the lack of primary trials supplied. The reference package contained review articles, one supplement which was sponsored by the company.

The clinical evidence is based on one trial, the EPIC trial. This was a well conducted, multi-centre, double blind, randomised, trial comparing abciximab with aspirin and heparin alone. The trial suggested an absolute reduction in a composite outcome of *death, non-fatal myocardial infarction or need for revascularisation at six months* of 8.1% (95% CI: 3.3%,13%) with the use of abciximab. The need for a revascularisation procedure by six months was 6.7% (95% CI:2.1%,11%) lower with abciximab than with placebo. **The trial, while well conducted, was relatively small and the confidence intervals around the estimates of effectiveness were wide. The results for the composite endpoint suggest that the number needed to be treated to gain one extra success is 12. This however could be as high as 30 due to the wide confidence interval.**

The major adverse effect of abciximab is bleeding with nearly twice the incidence of major bleeding compared to placebo. The excess bleeding was seen mainly in patients with a body weight <75kg and may have been due to the relatively high (and fixed) heparin dose used.

Economic Summary

The company undertook both a trial-based and model-based economic analysis looking at cost/effectiveness and cost/utility.

The trial-based analysis used the results from the pivotal study and estimated an incremental cost of \$17,791 per extra patient free of the composite endpoint at six months. The sensitivity analysis, using the lower 95% confidence limit for the difference in the composite endpoint, indicated that the incremental cost-effectiveness ratio could be as high as \$43,667 for each additional patient free of an event at 6 months.

The model-based analysis attempted to extrapolate survival, event free survival and QALYs over a 10 year period. The model was based on the initial 6 month data from the pivotal trial supplemented by data from two cohort studies examining survival, event-free survival and quality of life in patients with single and multi-vessel disease.

The cohort study in single vessel disease followed patients from 1977-1985 for 10 years. The cohort study in multi-vessel disease followed patients from 1983-1985 for only 5 years, then extrapolated the results out to 10 years. **There is some doubt as to the appropriateness of**

using these studies in constructing the model since the medical practices and the outcomes in these cohorts may not adequately reflect the experience of patients who are being treated currently. Essentially, the model assumes that subjects who have patent or occluded coronary vessels 6 months after treatment with abciximab experience the same patterns of subsequent care and the same outcomes as patients with these characteristics followed up in the cohort studies. This is not necessarily so.

In addition, the model assumed that any effects on morbidity or mortality due to the increased transfusion requirement seen with abciximab are only seen in the first six months and have no effect on long-term survival or morbidity. There is some suggestion that blood transfusions may be associated with increased long term morbidity and mortality.

The model based analysis suggested an incremental cost of \$7,665 per life year gained, a cost of \$ 5,858 per event-free year gained and \$ 9,639 per QALY gained.

Using National Heart Foundation data and data supplied to the Australian Health Ministers' Advisory Committee the estimated number of PTCAs to be performed in NSW in 1996 is between 4000 and 6310. Of these it is estimated that between 1680 and 2650 may fit the criteria for abciximab use. The estimated cost is therefore approximately \$2,500,000 but may be as high as \$4,000,000.

Overall, while the submission is well presented, there are concerns regarding the wide confidence intervals around the estimate of risk reduction. As a result, as many as 30 patients may require treatment to gain one extra success compared to current therapy. The total cost in NSW is estimated to be approximately \$2.5M in 1996 and much of this could be borne by a small number of hospitals that undertake frequent PTCAs.

1. INTRODUCTION

1.1 Pharmacology

Abciximab is a mouse-derived monoclonal antibody directed against the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor located on platelets. Abciximab inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive molecules to the GPIIb/IIIa receptor.

Human studies show that an initial bolus of 0.25mg/kg followed by a continuous infusion of 10mcg/min for a period of 12-96 hours produced a sustained receptor blockade (80%) of the GPIIb/IIIa. Low levels of receptor blockade are seen for periods of up to 10 days following stopping of the infusion, however bleeding times return to normal within 12-24hours of stopping the infusion in most patients.

Abciximab is given as an initial bolus of 0.25mg/kg followed by a continuous infusion of 10 mcg/min for 12 hours. The dose is the same for elderly patients.

Abciximab is indicated as adjunctive therapy for percutaneous transluminal coronary angioplasty (PTCA) and is used in conjunction with aspirin and heparin.

1.2 Adverse effects

The most common adverse effect of abciximab is bleeding. The pivotal study of abciximab plus aspirin/heparin vs aspirin/heparin alone (EPIC study group, 1994) indicated that major bleeding (as defined in the Thrombolysis in Myocardial Infarction [TIMI] trial) occurred in 14% of the patients receiving the suggested regimen (abciximab + aspirin/heparin) compared to 6.6% in those receiving aspirin/heparin alone. Of those receiving the suggested regimen, 16.9% had minor bleeding compared to 9.8% in the aspirin/heparin alone group. The majority of bleeding was at the femoral artery site and both groups had the same incidence of intracranial bleeding.

It should be noted that there was a significant increase in the need for transfusion in the abciximab group compared to placebo (aspirin/heparin alone) with 15% requiring transfusion in the abciximab group compared to 7% in the placebo group. It appears that bleeding tends to be greater in lower body weight patients (<75kg) and this may be related to the heparin dose. A decrease in the heparin dose in lighter patients may overcome this problem and this is being investigated in a follow up trial (EPILOG).

Other adverse effects reported include hypotension, nausea, vomiting, thrombocytopenia, haematoma, bradycardia, fever and vascular disorders.

1.3 Contra-indications

Abciximab is contraindicated in patients with a known sensitivity to abciximab. Due to its effects on platelets abciximab is contraindicated in patients with active internal bleeding, history of cerebrovascular accident within two years, intracranial or intra spinal surgery or trauma within two months, intracranial neoplasm, arteriovenous malformation or aneurysm, known bleeding diathesis, severe uncontrolled hypertension or pre-existing thrombocytopenia.

2. QUALITY OF FORMULARY SUBMISSION DOCUMENT

2.1 Clinical Data

The submission is largely based on the submission requirements for listing on the Pharmaceutical Benefits Scheme. The data is generally clearly presented and well referenced.

2.2. Economic Data

The data is again designed for the PBS submission. It therefore uses dispensed prices which are not relevant for the hospital setting. This does, however, overestimate the likely drug costs to the hospital.

2.3 References

The submission provides a 'package' of references. These are, however, only review articles of which one supplement is 'sponsored' by the company. The formulary submission, while containing a bibliography, does not provide the key clinical articles, in particular the EPIC trial. The literature search undertaken by the company appears thorough as no other relevant articles have been found by a search of Medline and EmBase.

3. MAIN THERAPEUTIC CLAIM

Abciximab is proposed to have a significant advantage over aspirin and heparin alone in reducing the risk of ischaemic complications including abrupt closure and re-stenosis following PTCA in high risk patients. High risk patients are defined as those who have unstable angina or a non-Q-wave myocardial infarction; an acute Q-wave myocardial infarction or; those with high risk clinical or morphological characteristics defined as either:

- Stenosis with two or more type B (AHA classification) lesions in the artery to be dilated, or
- Stenosis with one or more type C lesions in the artery to be dilated, or
- Age 65 years and female with at least one type B lesion in the artery to be dilated, or
- Diabetes mellitus and stenosis with at least one type B lesion in the artery to be dilated, or
- Angioplasty of an infarct-related lesion within 7 days of myocardial infarction

These are consistent with those recommended by the Australian Drug Evaluation Committee (ADEC) and are the inclusion criteria for the pivotal study (EPIC study group, 1994).

3.1 Clinical Studies

The pivotal study on which the trial-based evaluations are derived is the Evaluation of c7E3 Fab for Prevention of Ischaemic Complications (EPIC) trial.

The EPIC trial is a large, well conducted, prospective, double-blind, multi centre, placebo controlled trial (EPIC Investigators, 1994). The trial compared standard therapy (aspirin/heparin

alone) with either a single bolus injection of abciximab plus aspirin/heparin or an initial bolus followed by a continuous infusion of abciximab plus aspirin/heparin. Inclusion criteria were clearly stated and assessment of outcomes was decided *a priori* and measured in a blinded fashion. The initial trial assessed outcomes up to 30 days and a subsequent follow up assessed the outcomes at 6 months. Discontinuation rates were similar in all three arms.

Analysis of the results was done on an intention-to-treat basis with time-to-event measures used to assess the primary outcome(s). Continuous variables were analysed across the groups by non-parametric methods and tests for trends were done using analysis of variance. Odds ratios for the major outcome were calculated and Cox proportional hazards models were used to estimate possible associations between patient characteristics and outcomes.

The pivotal EPIC trial enrolled a total 2099 patients. Patient demographics were similar across the three groups with approximately 72% males and a median age of 61 years.

The results suggest a relative risk reduction in the composite outcome measure of 23% and an absolute risk reduction of 8.1% (95% CI 3.3%,13%) at six months. Repeat revascularization at six months was reduced from 29.4% in the placebo group to 22.7% giving an absolute risk reduction of 6.7% (95% CI 2.1%,11%).

Using the point estimate of the composite outcome, the number needed to treat to gain one extra success is 12. However, if the lower confidence interval estimate is used, this figure could be as high as 30.

The reported major adverse effects are as follows:

Event	Placebo	Bolus + Infusion
Haemorrhagic stroke	0.3%	0.4%
Non-haemorrhagic stroke	0.3%	0.3%
Major Bleeding with serious or life-threatening hypotension	1.1%	3.2%
Transfusion of >5 units of PRBC or whole blood, excluding CABG	0.4%	1.1%

The EPIC trial data at 30 days indicates that bleeding is increased, mainly at the femoral puncture site and that major bleeding and requirements for transfusions are double in the abciximab bolus + infusion arm:

Event	Placebo	Bolus + Infusion
Major Bleeding	6.6%	14%
Non CABG	3.3%	10.6%
Red Blood Cell Transfusion	7%	15%
Platelet transfusions	3%	6%

Despite this apparent increase in bleeding it did not result in increased mortality or morbidity. The bleeding complications have been studied further by the EPIC authors (Aguirre et al, 1995) and their results suggest that the major contributing factor to increased bleeding was low body

weight. This trial was a pilot for a larger study which has not been completed and thus has not been published.

The company has also sought to quantify the risk/benefit of the treatment by summing the benefits of treatment (MI, death and re-vascularisation avoided) and deducting the risks of treatment (major haemorrhage, thrombocytopenia, surgery for bleeding, haemorrhagic stroke, etc). The results suggest an attributable risk reduction of 7.4%

4. ECONOMIC CLAIMS

The company has undertaken two economic submissions; a trial-based evaluation based on the 6 month data of the EPIC trial and; a model-based evaluation to extrapolate survival, event free survival and QALYs gained. The analysis is therefore a cost-effectiveness/cost-utility analysis.

4.1 Trial Based Analysis

The submission has used the results from the EPIC trial to calculate total costs per patient, the cost-effectiveness and incremental cost for additional events avoided. While there are some apparent anomalies and errors in the reported costs, the approach to costing has generally been conservative as they have chosen the DRG costs of non-complicated procedures.

The results suggest a cost of \$5,630 per patient on placebo compared to \$7,064 for abciximab thus the incremental cost is \$1,441 per patient.

Based on the composite end point, the cost effectiveness ratio is \$ 8,674 for placebo compared to \$ 9,677 for abciximab giving an **incremental cost effectiveness for abciximab of \$ 17,791 for each additional patient without the composite endpoint at 6 months i.e. it will cost \$ 17,791 extra to for each additional patient without the endpoint at 6 months.**

The sensitivity analysis suggests that **the cost could be as high as \$43,667 for each additional patient free of the composite endpoint at 6 months** if lower value of the 95% confidence interval (3.3%) is used.

4.2 Model Based Analysis

The model-based analysis attempts to estimate the survival, event free survival and QALYs gained over a 10 year period after a successful PTCA. The model assumes that the excess rates of bleeding are short-term occurrences and are not relevant to the model. It should be noted that there is some evidence that blood transfusions may have an effect on increasing long term mortality (Vamvakas et al, 1995).

The model is based on two large cohort studies, one in single-vessel disease (Kadel et al, 1992) and one in multi-vessel disease (Vandormael et al, 1991).

Single-vessel disease

The study in single-vessel disease (Kadel et al, 1992) followed 798 patients for 78 ± 23 months who had PTCA between 1977 and 1985. The patients were younger (mean 53 years) than the

EPIC trial. Immediate success was similar to that found in the placebo arm of the EPIC trial. The model used the excess risk between those with unsuccessful PTCA compared to those with immediately successful PTCA to estimate the absolute risk reduction over time. The results are as follows:

Event	Successful PTCA	Unsuccessful PTCA
Survival at 10 years	92%	86%
Event free survival at 10 years	60%	15%

There is some doubt as to whether this data can represent current practice given the cohort was enrolled between 1977 and 1985.

Multi-vessel disease

The model data for multi-vessel disease came from another large cohort study (Vandormael et al, 1991) which followed 637 patients for 5 years. The paper only reported survival and not event free survival. Survival at 5 years was 88% if PTCA was successful and 77% if not. These rates were extrapolated for a further 5 years based on the average mortality from the first 2-5 years (approximately 1%). Once again these were entered in as life tables.

There is some doubt as to the appropriateness of using this data in the model since the actual cohort is only for 5 years not 10 and the data is extrapolated for years 5-10 from the 5 year data.

4.2.1 Results of the modelled analysis

The incremental analysis indicates the following:

	difference	cost
Cost per additional life year	0.188	\$ 7,665
Cost per additional event free year	0.246	\$ 5,858
Cost per additional QALY	0.1495	\$ 9,639

5. ESTIMATED USE

The company provides no actual figures for the anticipated use. The National Heart Foundation reports that there were 5,700 PTCA's performed in 1991 nationally and 8,334 in 1993. It could be expected that more than 10,000 will be performed in 1996. If it is assumed that 40% of Australia's population is based in NSW, then it is anticipated that 4,000 PTCAs will be performed in NSW in 1996. In a report by the Australasian Health Technology Advisory Committee to the Australian Health Ministers Advisory Council, it was estimated that 4020 PTCAs would be a conservative estimate of the number of PTCAs performed in NSW in 1996. The 'High' projection was 6310.

The company suggests that 42% of these represent the upper estimate for the number of patients who qualify for abciximab, then the projected number of patients in 1996 will be 1680 in NSW. Based on a wholesale cost of \$498.50 for one vial, and three vials being used per patient giving an average cost per patient of \$1495.50, the total estimated cost is \$ 2,512,440. If the 'High' projected figure from the report to AHMAC is used, this figure would be nearly \$4,000,000.

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