PUBLIC SUMMARY DOCUMENT

Product: Deferasirox, dispersible tablet, 125 mg, 250 mg and 500 mg, Exjade®

Sponsor: Novartis Pharmaceutical Australia Pty Limited

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought listing as a Section 100 (Highly Specialised Drug) for chronic iron overload associated with the treatment of disorders of erythropoiesis.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Exjade was registered by the TGA on 6 July 2006 for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults and paediatric patients 6 years and older. Exjade is also indicated for the treatment of chronic iron overload in paediatric patients aged 2 to 5 years who are unable to take desferrioxamine therapy or in whom desferrioxamine has proven ineffective.

4. Listing requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Private hospital authority required.
Chronic iron overload associated with the treatment of disorders of erythropoiesis.

The PBAC noted that in the Pre-PBAC response the sponsor was not opposed to a PBS restriction in alignment with the TGA registered indication.

5. Clinical place for the proposed therapy

Deferasirox is an oral treatment for patients with chronic iron overload secondary to transfusion dependent anaemias. It will provide an alternative to desferrioxamine, the current standard therapy in patients with chronic iron overload, which is delivered via subcutaneous infusion.

6. Comparator

The submission nominated desferrioxamine mesylate powder for injection as the comparator. The PBAC accepted that desferrioxamine is the appropriate comparator for first-line therapy in adults and children>6 years, however, for children 2-5 years the comparator could also be deferiprone.

7. Clinical Trials

The submission presented three head-to-head randomised comparative trials comparing deferasirox and desferrioxamine:

(i) Trial 107 – a randomised, comparative, open label phase III, non-inferiority trial of efficacy and safety of long-term treatment with deferasirox (5 to 40mg/kg/day) in comparison with desferrioxamine (20 to 60mg/kg/day) in β-thalassemia patients with transfusional hemosiderosis.

(ii) Trial 109 – a randomised, multicentre, open label, phase II study evaluating the safety, tolerability, pharmacokinetics and the effects on liver iron concentration (LIC) of repeated doses of 10mg/kg/day of deferasirox relative to desferrioxamine in patients with sickle cell disease and transfusional haemosiderosis

(iii) Trial 105 – a randomised, open label, phase IIa study evaluating the safety, tolerability and the effects on liver iron concentration of repeated doses of 10 and 20mg/kg/day of deferasirox in comparison with 40mg/kg/day desferrioxamine in patients with thalassaemia and transfusion dependent iron overload.

Two of these trials had been published at the time of the submission:

Trial/First author	Publication title	Publication citation
Trial 107/ Cappellini MD et al.	Phase III evaluation of once-daily, oral therapy with ICL670 versus desferrioxamine in patients with β-thalassaemia and transfusional hemosiderosis.	Poster No. 3619, American Society of Hematology, Annual Conference, San Diego California, December 2004. Published in abstract form in Blood, 2004; 104 (11 Suppl) Abs 3619.
Cappellini MD et al.	A Phase III study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β-thalassemia.	Blood First Edition Paper 2005; 13 December Dec 15: 1-33.
Trial 105/ Piga A et al.	Phase II study of ICL670, an oral chelator, in adult thalassaemia patients with transfusional iron overload: efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) after 18 months of therapy.	Blood 2003; 102: 11 (Pt 1): 121a).
Piga A et al	Phase II study of oral chelator ICL670 in thalassaemia patients with transfusional iron overload: Efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) after 6 months of therapy.	Blood (2002): 100 (11/1): 5a

8. Results of Trials

The results showed that based on the overall assessment, treatment with deferasirox did not meet the pre-specified non-inferiority criterion. Deferasirox was significantly less effective than desferrioxamine in the overall intention-to-treat (ITT) population. However, in the subgroup of patients with a baseline liver iron concentration (LIC) ≥7mg/Fe/g dw (that is, those receiving 20mg/kg to 30mg/kg deferasirox), comprising 68% of the trial population, the pre-specified non-inferiority criteria were met.

The results for the secondary efficacy outcome for patients in the LIC <7mg Fe/g dw group were significantly different between deferasirox and desferrioxamine. In this patient group with LIC <7mg Fe/g dw, both primary (success rate) and secondary

(changes in LIC) outcomes showed that desferrioxamine was better. However, for the overall population (ie both LIC <7 and LIC >7 mg Fe/g dw), the secondary outcome (changes in LIC) showed no significant difference between desferrioxamine and deferasirox.

In regards to safety, treatment with deferasirox appeared to be associated with an increased risk of hepatobiliary disorders and elevated creatinine levels (Trials 107 and 109; not reported for Trial 105).

9. Clinical Claim

The submission described deferasirox as being no worse than desferrioxamine in terms of effectiveness and toxicity. The average doses administered in Trial 107 were desferrioxamine: 43.8 mg/kg and deferasirox: 19.9 mg/kg.

The submission, in Section 3 (modelled evaluation) claimed that although deferasirox is no worse than desferrioxamine in terms of efficacy and safety, deferasirox was associated with additional benefits (increased quality of life due to differences in mode of administration and increased compliance) that were not captured in the trials.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

The submission provided estimates of annual cost of treatment with desferrioxamine and deferasirox assuming 100% compliance. On the basis of annual drug costs, deferasirox was a more expensive treatment than desferrioxamine.

A modelled economic evaluation was presented to incorporate benefits of deferasirox not captured by the trials. The choice of the cost- utility approach was valid only if the PBAC accepted that deferasirox had advantages over desferrioxamine in terms of quality of life and that deferasirox was no worse in terms of efficacy and safety than desferrioxamine.

The resources included were drug costs and costs of treating complications of chronic iron overload. The base case modelled incremental discounted cost per extra QALY gained over 100 years was in the range of $15,000 – $45,000. The ESC advised of uncertainty in the modelled economic evaluation associated with the assumption of the average age of patients at baseline, and the estimate of a 28% reduction in utility for iron chelation via subcutaneous infusion compared with oral therapy.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was < 10,000 in Year 4 of listing, while the financial cost per year to the PBS was < $10 million in Year 4 listing.

12. Recommendation and Reasons:

The PBAC recommended listing on a cost effectiveness basis versus the comparator, desferioxamine, noting however that the incremental cost-effectiveness ratio is somewhat uncertain and is likely to be high.

The PBAC noted that the ITT data from the key trial (107) did not support a conclusion that deferasirox was non-inferior to the comparator, desferioxamine (non-inferiority was considered to be established if two-sided 95% confidence interval for the difference in success rate (deferasirox-desferrioxamine) was above -15%). In the subgroup of patients with a baseline liver iron concentration (LIC) ≥7mg/Fe/g dw, comprising 68% of the trial population, the pre-specified non-inferiority criteria was met. The PBAC accepted that the failure to meet the pre-specified non-inferiority criteria in the ITT population may have been due to an underdosing of deferasirox relative to desferrioxamine in the group with a baseline LIC < 7mg/Fe/g dw. Data provided in the Pre-PBAC Response indicate that at the end of the trial the deferasirox to desferrioxamine dose relativity in the < 7 mg/Fe/g dw group was 1:3.4 compared to 1:2.0 for the >7mg/g subgroup. Although this observation did not provide a definitive explanation, it removed considerable uncertainty. The PBAC accepted that, on balance, the non-inferiority of deferasirox had been demonstrated.

The Committee agreed with the ESC advice that there were two critical issues of uncertainty in the modelled economic evaluation provided. These were the average age at baseline of the modelled cohort and the extent of the utility gain. Although the base case incremental cost per quality adjusted life year (QALY) appeared reasonable at $36,420 it could increase to around $60,000 per QALY if the starting age was increased to 17 or the utility gain was lower. The PBAC therefore acknowledged there is some uncertainty about the base-case ICER. The Committee however agreed that there is a clinical need for a safe and effective oral agent for the management of iron overload in this orphan indication and that it could be predicted that the quality of life for these patients would be significantly enhanced by the availability of an oral agent, and listing was recommended.

The PBAC requested that the DUSC monitor the uptake and continuing usage of deferasirox.

Recommendation

Deferasirox, dispersible tablets, 125 mg, 250 mg and 500 mg

Restriction: Private hospital authority required (Highly Specialised Drug)
Chronic iron overload in adults, adolescents and children 6 years and older associated with disorders of erythropoiesis;
Chronic iron overload in paediatric patients age 2 to 5 years, associated with disorders of erythropoiesis, who are intolerant to desferrioxamine or in whom desferrioxamine has proven ineffective.

Pack size: 28

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend

listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis hopes that the availability of Exjade will allow those who suffer from chronic iron overload a better quality of life with this once-daily oral iron chelator. Novartis would like to thank the PBAC for its consideration and subsequent recommendation of Exjade to be listed on the PBS.