

### 3.1 IRON CHELATING AGENTS

**DEFERASIROX, tablets, 125 mg, 250 mg, 500 mg, Exjade<sup>®</sup>, Novartis Pharmaceuticals Australia Pty Ltd,**

**DEFERIPRONE, oral liquid, 100 mg/mL, 250 mL, tablet, 500 mg, Ferriprox<sup>®</sup>, Orphan Australia Pty Ltd,**

**DEFERRIOXAMINE, injections, 2 g vial and 500 mg vials, Desferal<sup>®</sup>, Novartis Pharmaceuticals, Hospira brand product, Hospira Pty Ltd**

#### 1 Purpose of Application

- 1.1 To consider if further review of the iron chelating agents is required.
- 1.2 Following the update given to the PBAC at its March 2014 meeting on the results of the DUSC analysis on iron chelating agents in February 2014, the PBAC requested further information to inform this decision.

#### 2 Background

- 2.1 At its March 2014 meeting the PBAC was provided with a verbal update of the results of the utilisation analysis on iron chelating agents undertaken by the DUSC at its February 2014 meeting.
- 2.2 Key findings of the analysis included:
  - Use of desferrioxamine and deferiprone is declining, while use of deferasirox, particularly the 500mg strength, is increasing.
  - The DUSC considered that utilisation of deferasirox for myelodysplastic syndromes (MDS) may be higher than expected at the time of PBS listing. Most of the patients on deferasirox treatment are over 55 years of age indicating use for MDS rather than thalassaemia due to the high level of childhood mortality from thalassaemia prior to the 1960s.
- 2.3 The PBAC requested that the clinical and economic basis for the PBAC recommendation to list deferasirox be provided to the committee along with the full DUSC analysis to allow the committee to recommend if further review is required.
- 2.4 A copy of the Public Release Document for iron chelating agents from the February 2014 DUSC meeting is available at

*Public Summary Document- November 2014 PBAC Meeting*

<http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/iron-chelating-agents-2014>.

- 2.5 At its July 2006 meeting, the PBAC recommended the listing of deferasirox on a cost effectiveness basis versus the comparator, desferrioxamine. The PBAC noted that the incremental cost-effectiveness ratio was somewhat uncertain and was likely to be high. It was noted that the average age at baseline of the modelled cohort and the extent of the utility gain were the two critical areas of uncertainty in the modelled economic evaluation of deferasirox. The base case, with an average starting age of 5 years, had an incremental cost-effectiveness ratio (ICER) of \$36,420 per quality adjusted life year (QALY). This increased to around \$60,000/QALY if the starting age was increased to 17 or the utility gain was lower. The PBAC therefore acknowledged there was some uncertainty about the base-case ICER.
- 2.6 The Committee agreed that there was a clinical need for a safe and effective oral agent for the management of iron overload and predicted that the quality of life for these patients would be significantly enhanced by the availability of an oral agent.
- 2.7 A copy of the Public Summary Document from the July 2006 PBAC meeting is available at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2006-07/deferasirox>.
- 2.8 The July 2006 PBAC submission presented three head-to-head randomised comparative trials comparing deferasirox and desferrioxamine:
1. 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 beta-thalassemia patients with transfusional hemosiderosis.
  2. 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
  3. 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.
- 2.9 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)  $\geq 7\text{mg/Fe/g dw}$  (that is, those receiving 20mg/kg to 30mg/kg deferasirox), comprising 68% of the trial population, the pre-specified non-inferiority criteria were met.
- 2.10 The results for the secondary efficacy outcome for patients in the LIC  $< 7\text{mg Fe/g dw}$  group were significantly different between deferasirox and desferrioxamine. In this patient group with LIC  $< 7\text{mg Fe/g dw}$ , both primary (success rate) and secondary

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

- 2.11 The July 2006 PBAC submission presented a modelled economic evaluation to incorporate benefits of deferasirox not captured by the trials. This approach was based on accepting that Trial 107 demonstrated that deferasirox had similar efficacy and safety to desferrioxamine, and that the use of deferasirox is associated with additional benefits that were not captured in the trials. These include:

[REDACTED]

- 2.12 The ESC noted that the choice of the cost-utility approach was valid only if it was 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.

[REDACTED]

- 2.13 The resources included were drug costs and costs of treating complications of chronic iron overload. The overall comparative costs and outcomes for each alternative and the incremental costs and outcomes are summarised below.

Base case results of the modelled incremental analysis

	Outcomes over 100 years		Diff. deferasirox vs desferrioxamine
	deferasirox	desferrioxamine	
Total Costs, disc	[REDACTED]	[REDACTED]	[REDACTED]
Life years, disc.	[REDACTED]	[REDACTED]	[REDACTED]
QALYs, disc.	[REDACTED]	[REDACTED]	[REDACTED]

- 2.14 The base case modelled incremental discounted cost per extra QALY gained over 100 years was in the range of \$15,000 – \$45,000.

- 2.15 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.

### **3 PBAC Outcome**

- 3.1 The PBAC considered the findings of the DUSC review of iron chelating agents, noting that the use of deferasirox, in particular 500 mg deferasirox, is much higher than that estimated at the time of PBS listing. The PBAC also noted that 59 % of patients receiving an iron chelating agent in the second quarter of 2013 were over 55 years of age. The PBAC agreed with the DUSC that a considerable proportion of the PBS utilisation of deferasirox is likely to be for myelodysplastic syndromes (MDS), rather than for thalassaemia, given the proportion of use in patients over the age of 55, and the high proportion of use in males over the age of 55.
- 3.2 The PBAC considered that the use of deferasirox in MDS is controversial and its clinical place in MDS is unclear. Noting that it has never received an application for PBS-listing of deferasirox for this indication, the PBAC requested that clinical advice be sought on the use of iron chelating agents, in particular deferasirox, in MDS and other malignant haematological diseases associated with chronic transfusions from relevant professional bodies including the Haematological Society of Australia and New Zealand, the Australian and New Zealand Childrens Haematology/ Oncology Group and the Royal College of Pathologists of Australasia. Key information requested from these organisations includes (i) definition of which patients may benefit; (ii) what the benefits are and the evidence for these benefits; and (iii) the utility of standard tests such as serum iron studies and serum ferritin to inform treatment decisions about iron chelation.
- 3.3 The PBAC recalled that its decision to recommend the listing of deferasirox in July 2006 was based on evidence predominantly of use in thalassaemia. The PBAC also noted that the cost effectiveness of deferasirox was greatly affected by the age of onset and the 100 year time horizon used in the economic modelling. As the age of onset and the time horizon for patients with MDS are substantially different to those of patients with thalassaemia used in the original economic model, and that the direction of change must increase the incremental cost effectiveness ratio, the PBAC considered that the use of deferasirox in MDS has not been shown to be cost effective. The PBAC hence recommended that the PBS restriction for deferasirox be amended to: Chronic iron overload in patients with non-malignant disorders of erythropoiesis. Given the apparent widespread use beyond the intended original restriction, the PBAC recommended that the restriction category for deferasirox be changed to a written authority for the initial use, with a telephone authority required listing for continuing use.
- 3.4 The PBAC noted that the sponsor may submit an application to the PBAC to extend the listing of deferasirox to include MDS and other malignant haematological diseases associated with chronic transfusions with evidence to support the clinical efficacy and safety and cost effectiveness in this indication.

#### **Outcome**

Recommend.

#### 4 Recommended listing

4.1 Amend the existing listing of deferasirox as follows:

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty Units	№.of Rpts	Proprietary Name and Manufacturer	
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DEFERASIROX

Deferasirox 125 mg tablet: dispersible, 28	6	168	5	Exjade	NV
Deferasirox 250 mg tablet: dispersible, 28	6	168	5	Exjade	NV
Deferasirox 500 mg tablet: dispersible, 28	6	168	5	Exjade	NV

<b>Condition:</b>	Chronic iron overload
<b>Restriction:</b>	Authority Required – In writing
<b>Treatment phase:</b>	Initial treatment
<b>Clinical criteria:</b>	Patient must be transfusion dependent.  AND:  Patient must not have a malignant disease.

<b>Condition:</b>	Chronic iron overload
<b>Restriction:</b>	Authority Required – telephone
<b>Treatment phase:</b>	Continuing treatment
<b>Clinical criteria:</b>	Patient must be transfusion dependent.  AND:  Patient must not have a malignant disease.

**5 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.

**6 Sponsor's Comment**

Novartis intends to submit a cost effectiveness submission to retain reimbursed access to deferasirox for MDS patients to the first available PBAC cut off.

The other sponsors had no comment.