Scottish Medicines Consortium

deferasirox, 125, 250, 500mg dispersible tablets (Exjade®) No. (347/07)

Novartis Pharmaceuticals UK Limited

12 January 2007

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

ADVICE: following a full submission

deferasirox (Exjade®) is accepted for restricted use within NHS Scotland for the treatment of chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions. It is not recommended for patients with myelodysplastic syndromes.

Patients with myelodysplastic syndromes, the commonest cause of transfusion-dependent anaemia, were poorly represented in the clinical trial population and the economic case was not demonstrated in this group.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of chronic iron overload due to frequent blood transfusions (≥ 7ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older; and treatment of chronic iron overload due to blood transfusions when desferrioxamine therapy is contraindicated or inadequate in the following patient groups: patients with other anaemias; patients aged 2-5 years; patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (< 7ml/kg/month of packed red blood cells).

Dosing information

The usual recommended initial daily dose is 20mg/kg body weight. The maintenance dose should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of iron burden) by adjusting the dose in steps of 5 to 10mg/kg if necessary, every three to six months according to trends in serum ferritin. Daily doses above 30mg/kg are not recommended.

Product availability date

September 2006

Summary of evidence on comparative efficacy

Frequent blood transfusions are required to treat certain hereditary and acquired anaemias. As there is no natural mechanism to excrete excess iron, this leads to a potentially fatal accumulation necessitating iron chelation treatment. Deferasirox is a once daily oral tridentate iron-selective chelator which was granted orphan drug status in the European Union in 2002.

The pivotal phase III open-label study randomised 586 patients aged ≥ 2 years, with beta-thalassaemia major and transfusional iron overload requiring ≥ 8 blood transfusions per year and with a liver iron concentration (LIC) ≥ 2mg iron per gram dry weight (Fe/g dw). LIC reflects total body iron status. Patients naive to iron chelation or already receiving desferrioxamine (DFO) treatment were randomised in a 1:1 ratio to deferasirox 5, 10, 20 or 30mg/kg orally once daily or DFO 20-30, 25-35, 35-50, >50mg/kg as a subcutaneous infusion over 8-12 hours on five consecutive days each week, with doses assigned according to baseline LIC: (≤ 3; >3-7; >7-14; >14) mg Fe/g dw. The primary efficacy objective was to show non-inferiority of deferasirox to DFO, after one year of treatment, with respect to the effect on LIC as assessed by liver biopsy or superconducting quantum interference device (SQUID); an unvalidated, non-invasive technology. The criterion for success was dependent on LIC at baseline. The primary efficacy population comprised patients with LIC at baseline and end of study, assessed using the same technique, and those that discontinued for safety reasons.

Success rates in the primary efficacy population

	deferasirox	desferrioxamine
All LIC values	n=276	n=277
Success rate no. (%)	146 (52.9)	184 (66.4)
95% CI	47.0, 58.8	60.9, 72.0
Difference (deferasirox-DFO); 95% CI	-13.5 [-21.6, -5.4]	
LIC below 7mg Fe/g dw	n=85	n=87
Success rate no. (%)	34 (40.0)	72 (82.8)
95% CI	29.6, 50.4	74.8, 90.7
Difference (deferasirox-DFO); 95% CI	-42.8 [-55.9, -29.7]	
LIC at least 7mg Fe/g dw	n=191	n=190
Success rate no. (%)	112 (58.6)	112 (58.9)
95% CI	51.7, 65.6	52.0, 65.9
Difference (deferasirox-DFO); 95% CI	-0.3 [-10.2, 9.6]	

CI = confidence interval; Fe/g dw = iron per gram (dry weight)

The primary analysis of the primary efficacy population, (276 in the deferasirox group and 277 in the DFO group), failed to demonstrate non-inferiority of deferasirox to DFO: difference and 95% confidence interval (CI) -13.5 [-21.6, -5.4]. In a post-hoc subgroup analysis of patients with baseline LIC ≥7mg Fe/g dw, ie those treated with deferasirox (20 and 30mg/kg) or desferrioxamine (35 to ≥50mg/kg), the non-inferiority criteria were achieved. In patients with less severe iron overload (<7mg Fe/g dw as baseline), receiving relatively fewer blood transfusions, the non-inferiority of deferasirox compared to desferrioxamine was not established. However the deferasirox doses in this group were very low; 5mg/kg is unlicensed and 10mg/kg is only used in specific circumstances.

An imbalance in the dosing of the two drugs because patients on desferrioxamine were allowed to remain on their pre-study dose even if it was higher than the protocol-specified dose may have favoured the results in patients (especially those less severely overloaded) treated with DFO. The actual dose of DFO often exceeded the dose initially allocated, precluding a fair comparison between the two treatments which could partly explain the failure to achieve non-inferiority. About 84% of patients in the DFO group received the two higher doses of DFO (35 to ≥50mg/kg of DFO) compared to about 69% of patients in the two highest deferasirox dose groups (20 or 30mg/kg).

An uncontrolled phase II open-label efficacy study recruited 85 patients with beta-thalassaemia and transfusional iron overload who could not be properly chelated with DFO, and 99 patients with a variety of acquired or hereditary rare anaemias, including myelodysplastic syndrome, (MDS), Diamond Blackfan anaemia and aplastic anaemia, requiring chelation therapy. Deferasirox treatment was as detailed in the pivotal study. The primary objective, to evaluate the effects of deferasirox treatment on changes in LIC as assessed by liver biopsy or SQUID after one year, defined chelation therapy as effective if the lower limit of the 95% CI for success rate exceeded 50%. This was not achieved for the intention to treat population. In the subgroup treated with deferasirox at doses of 20 and 30mg/kg/day, (corresponding to a baseline LIC of ≥ 7mg Fe/g dw as assessed by biopsy), success in the reduction in LIC was shown in 59% of patients.

The efficacy of deferasirox was considered established in patients with moderate to severe iron overload, receiving frequent blood transfusions. There was a clinically meaningful stabilisation and/or reduction in LIC over a one year period of treatment with deferasirox 20-30mg/kg/day. Lower doses did not appear to be beneficial. The degree of reduction was dependent on the quantity of blood transfusions required for the continuing therapy of the anaemia.

Summary of evidence on comparative safety

In the pivotal study, overall adverse event rates in the deferasirox and DFO groups (85.8% vs 84.8% respectively) were similar. Those reported more frequently in the deferasirox group were abdominal pain (13.9% vs 9.7%), diarrhoea (11.8% vs 7.2%), nausea (10.5% vs 4.8%), creatinine increase (11.1% vs 0%), rash (8.4% vs 3.1%), upper abdominal pain (7.8% vs 5.2%), arthralgia (7.4% vs 4.8%), acute tonsillitis (6.4% vs 5.2%), fatigue (6.1% vs 4.8%), dyspepsia (3% vs 1.7%) and hepatobiliary disorders (4.7% vs 1.7%). Infusion site reactions were prominent among DFO patients. Serious adverse event rates were (9.1% vs 8.6%) in the deferasirox and DFO groups respectively.

Pooled safety data showed that serum creatinine increases of 30% to >90% occurred early, in general within the first month of treatment with deferasirox, and were dose dependent. In 50% of patients, the serum creatinine values only stabilised after dose reduction. The long term consequences of the renal toxicity of deferasirox are unknown.

A phase II randomised, controlled, open-label safety trial in patients with sickle cell disease and transfusional iron overload requiring chelation therapy found deferasirox was well tolerated with a similar adverse events profile to the pivotal study. Serious adverse events reported were 34.8% and 33.3% in the deferasirox and DFO groups respectively.

Summary of clinical effectiveness issues

MDS patients constitute the largest group of patients in Scotland with transfusion-dependent anaemias and these patients were not included in the pivotal trial. Throughout the whole clinical trial program, only 47 MDS patients have been studied in an uncontrolled efficacy study. It is not clear that the problems of iron overload and possible effectiveness of iron chelation therapy is the same in MDS as in other transfusion-dependent anaemias. Only a small minority of patients with MDS in Scotland appear to be currently treated with iron chelation therapy.

The scientific discussion of the European Public Assessment Report notes that in patients with anaemias other than beta thalassaemia major (i.e. sickle cell disease, myelodysplastic syndrome or rare anaemias) the efficacy of deferasirox could not be robustly extrapolated from the weak evidence obtained from the pivotal study. This may affect the generalisability of results to the Scottish population.

In the trial program LIC was measured by biopsy or SQUID. Biopsy cannot be used routinely to monitor iron burden, particularly in the paediatric population. SQUID is an unvalidated method which seems to underestimate LIC. Serum ferritin is normally used in practice to estimate the degree of iron overload, although the correlation is imperfect.

Available trial data do not allow for a conclusion regarding effects of deferasirox on morbidity or mortality.

Safety data are limited. A risk management plan is to be set up to address the following safety concerns: serum creatinine increases, elevations of liver transaminases, high frequency hearing loss, lenticular opacities and cataracts, cardiac monitoring in cardiac iron overload, limited experience in paediatric patients between 2 and 6 years, limited experience in renal and hepatic impairment. Renal disorders observed in the overall population remain a concern in the very young. Although deferasirox was not associated with growth disorders,

caution should be exercised due to the small number of paediatric patients and the short treatment duration.

The formulation of deferasirox as an oral dispersible tablet is likely to significantly improve quality of life and patient compliance in all age groups compared with the current treatment of choice, desferrioxamine, which requires subcutaneous infusion over 8-12 hours, 5 to 7 times a week. For most patients, deferasirox is only indicated where desferrioxamine is contra-indicated or insufficiently effective.

Summary of comparative health economic evidence

The manufacturer used the sub-group analysis of the 2/3 of patients with LIC ≥ 7mg Fe/g dw within the pivotal trial to justify equivalent clinical effectiveness between deferasirox and subcutaneous desferrioxamine. Subcutaneous desferrioxamine is an appropriate comparator, and for the trial sub-group clinical equivalence was justified. The analysis took account of:

- the direct drug costs,
- the costs of administration,
- the costs of adverse events,
- the quality of life impact from the convenience of administration in terms of the oral formulation, and
- the quality of life impact from adverse events

The original submission stated that with current therapy 79% of patients received treatment using a balloon infuser. However, feedback from Scottish experts suggested that the figure was considerably lower. This assumption reduced the cost of current treatment and therefore increased the cost per QALY of deferasirox. Revised figures from the company assuming much lower levels of balloon infuser use were provided. In patients with β-thalassaemia the cost per QALY was around £20000, in patients with sickle cell disease (SCD) it was around £30000, and in patients with MDS it was over £38000 per QALY. All of these figures are in comparison with desferrioxamine.

On this basis the cost-effectiveness of deferasirox was acceptable in patients with β-thalassaemia and with SCD but the case has not been demonstrated in patients with MDS. An additional factor in patients with MDS was that it is not clear that desferrioxamine was the most appropriate comparator treatment.

Summary of patient and public involvement

Patient Interest Group Submission: The Sickle Cell Society
Patient Interest Group Submission: United Kingdom Thalassaemia Society

Additional information: comparators

Desferrioxamine has been in use for about forty years and remains the standard chelation therapy for the removal of excess iron.

Due to the limited efficacy and safety data and especially the risk of agranulocytosis, the oral iron chelator deferiprone is licensed only for the treatment of iron-overloaded thalassaemic

patients when treatment with desferrioxamine is contraindicated or inadequate and is therefore not considered a comparator for this submission.

Additional information: costs

Product	Regimen	Cost per year (£)
deferasirox	**20-30mg/kg daily**	**15,288-30,576**
desferrioxamine	20-60mg/kg daily for 5 to 7 days/week	3,464-16,169

Costs accessed from eVadis database on 30th October 2006. Costs based on adult body weight range 60-80kg., however a substantial proportion of this patient population are children. Doses are shown for general comparison and do not imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimated that around 190 patients were receiving iron chelation in Scotland: 19 beta-thalassaemia, 7 sickle cell and 166 MDS patients. Based upon a market penetration of 30% in year 1 rising to 70% by year 5, the gross drug costs were estimated as £1.0 million in year 1 rising to £2.5 million by year 5. However, this estimate includes patients with MDS. Removal of the MDS group would reduce the budget impact significantly.

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 December 2006.

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.

Cappellini MD, Cohen A, Piga A, et al A phase 3 study of deferasirox (ICL670), a once daily oral iron chelator, in patients with beta-thalassaemia. Blood 2006; 107 (9) 3455-3462.

Porter J, Vichinsky E, Rose C, et al. A phase II study with ICL670 (Exjade®), a once daily oral iron chelator, in patients with various transfusion-dependent anaemias and iron overload. Abstract 3193. 46th American Society of Haematology meeting, San Diego USA,4th-7th December 2004.

Vichinsky E, Fischer R, Gabellini A, et al. A randomised, controlled phase II trial in sickle cell disease patients with chronic iron overload demonstrates that the daily oral iron chelator deferasirox (Exjade®, ICL670) is well tolerated and reduces iron burden. Abstract 313. 47th American Society of Haematology meeting, Atlanta USA, 10th -13th December, 2005.