For Information
On 24 June 2008

Legislative Council Panel on Health Services

Iron chelating therapy for Thalassaemia patients in public hospitals

PURPOSE

This paper briefs Members on the iron chelating therapy for Thalassaemia patients provided by public hospitals.

BACKGROUND

2. Thalassaemias major are inherited blood disorder affecting the red blood cells. Red blood cells contain haemoglobin with iron inside that is responsible for carrying oxygen for our body needs. Thalassaemia causes the body to make fewer healthy red blood cells and the abnormal red blood cells will also be broken down more frequently by the body. As a result, the oxygen carrying capacity of the red blood cells is impaired.

3. The standard treatment for Thalassaemias is regular blood transfusion to replenish red blood cells. Patients usually require a transfusion every few weeks. In between the blood transfusion, the red blood cells are broken down slowly by the body. However, the iron will stay in the body after the red blood cells have been broken down. As there is no natural means for the body to remove the excessive iron, Thalassaemia patients who are receiving blood transfusion must undergo treatment to remove the excessive iron from their body, otherwise, the accumulation of iron in the internal organs such as the heart, liver and endocrine glands will eventually result in multiple organ dysfunctions. This iron removal treatment is known as iron chelating therapy.

4. There are three chelating agents available in the Hospital Authority (HA), namely Desferrioxamine, Deferiprone and Deferasirox.

Desferrioxamine (DFO)

5. DFO works by locking onto, or binding, the iron molecules in the body, and then releasing them through urine or stools. DFO is usually administered by using a pump that slowly feeds the medicine through a needle into the skin. This route is known as a subcutaneous transfusion. This form of treatment needs to be provided to a patient five to seven times a week. Each transfusion will take 8 to 12 hours. The chelating agent has been in the market for more than 40 years and is manufactured by Novartis.

Deferiprone

6. Deferiprone is used as a second-line treatment in patients with Thalassaemia major for whom DFO therapy is contraindicated, intolerant or non-compliant. This is an oral medication to be administered three times daily. The drug has been in the market since August 1999 and is manufactured by Apotex.

Deferasirox

7. Deferasirox is an oral iron chelating agent to be administered once daily. It is currently classified as a self-financed item in HA. This drug was put to market in November 2005 and is manufactured by Novartis.

8. A table summarizing the three drugs, including their efficacy, side effects and costs etc. is at **Annex**.

INTRODUCTION OF DRUGS INTO HA

9. Rapid advances in medical technology bring many new drugs into the pharmaceutical market every year. The decision to introduce individual drugs into the HA Drug Formulary (the Formulary) involves evaluation of scientific evidence, clinical ethics and complex clinical decisions, as well as professional discussions and deliberations. Furthermore, comparison of new modality of treatment with the existing regime requires a solid medical background.

10. To ensure that public resources are utilized in the most equitable and effective way and that HA can provide services to the largest possible number of patients with the limited resources, the decision on whether a drug should be covered by HA's standard treatment has to be made on the basis of clinical efficacy, safety, cost effectiveness and opportunity cost.

11. While most of the drugs provided by HA are highly subsidized by the Government and included in the Formulary, three main types of drugs have to be self-financed by patients without subsidy. These include:

(a) drugs which have preliminary medical evidence only;
(b) drugs with marginal benefits over available alternatives; and
(c) lifestyle drugs.

12. When considering the positioning of the above-mentioned three chelating drugs in the Formulary, the aforesaid guiding principles of clinical efficacy, safety, cost effectiveness, and opportunity cost as well as facilitation of patients' choice apply. Both DFO and Deferiprone are currently covered by HA's highly subsidized scope of standard treatment. DFO is classified as a General Drug while the oral drug Deferiprone is available as a Special Drug. As far as Deferasirox is concerned, the drug is of preliminary medical evidence and marginal benefits, and is substantially more expensive than the other two. Furthermore, there were also reports of possible severe side effects and fatal complications in post market surveillance. It is currently available in HA as a self-financed item since April 2007.

SUMMARY

13. We appreciate that patients will have natural aspiration for specific drugs to be included as standard treatment in the Formulary. In this regard, HA has maintained regular communication with patient groups to understand and address their concerns about introduction of new drugs into the Formulary through our long established liaison channel to ensure that their views are well represented. However, it is prudent for HA to rationally deploy the finite public resources to best serve the needs of the community. HA will continue to review constantly the Formulary to ensure a constant appraisal of new drugs in

relation to available alternatives, good standard of medical practice, delivery of effective treatment to patients and rational use of resources.

ADVICE SOUGHT

14. Members are invited to note the content of this paper.

Food and Health Bureau
Hospital Authority
June 2008

Annex

A summary of the features of Desferrioxamine, Deferiprone and Deferasirox
(Note: The summary is compiled on the basis of the list of references at Appendix.)

	Desferrioxamine (Desferal®)	**Deferiprone (Ferriprox®)**	**Deferasirox (Exjade®)**
Manufacturer	Novartis	Apotex	Novartis
Licensed indication	Treatment for chronic iron overload, e.g. - -transfusional haemosiderosis in patients receiving regular transfusions (e.g. thalassaemia major). - primary and secondary haemochromatosis in patients in whom concomitant disorders (e.g. severe anaemia, cardiac disease, hypoproteinaemia) preclude phlebotomy.	Treatment of iron overload in patients with thalassaemia major when desferrioxamine therapy is contraindicated or inadequate.	Treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in patients 2 years of age and older
Route of administration	slow subcutaneous infusion over 8-12h, 5-7 times a week	oral, three times a day	oral, once daily
Dosage (licensed age)	20-60mg/kg/day for <3 year old (max. 40mg/kg)	25mg/kg three times daily for aged ≥6 years	20-30mg/kg/day aged ≥ 2 years
Year on market	>40 years ago	Aug 1999 (2004 in HA)	Nov 2005 (2007 in HA)
Efficacy	- current standard iron chelator - improves hepatic, cardiac, and endocrine dysfunction	<u>From Cochrane review</u> - both deferiprone and desferrioxamine significantly reduced iron stores	- in randomised non-inferiority, phase 3 one-year multicentre open-label trial (n= 586):

	Desferrioxamine (Desferal®)	Deferiprone (Ferriprox®)	Deferasirox (Exjade®)
		- no evidence to suggest that either was more clinically efficacious.	52.9% deferasirox (oral 5-30mg/kg) versus 66.4% desferrioxamine(sc 20-60mg/kg 5 times per wk) responded to treatment.
		<u>From individual studies</u> - Deferiprone is comparable with desferrioxamine as monotherapy over a 1 year - deferiprone may remove myocardial iron more effectively than desferrioxamine - cardiac disease free survival over 5 years was more favourable with deferiprone versus desferrioxamine. - long-term studies show that liver iron is not adequately controlled by deferiprone monotherapy in a significant proportion of patient - anecdotal evidence of improved compliance in those who have difficulties with desferrioxamine but Cochrane review found no major differences in compliance between deferiprone & desferrioxamine (all achieved good to excellent compliance).	- indicating deferasirox may not have been as effective as desferrioxamine. - However, in sub-group analysis of the 381 pt who had particularly high levels of iron in the liver (Liver Iron Concentration >7mg Fe/g dry weight) at the start of study, including paediatrics at 30mg/kg/day receiving comparable doses of deferasirox or desferrioxamine, both medicines were as effective. - 20mg/kg/day deferasirox ↓ iron burden but this may not be comparable to reduction shown with desferrioxamine - no information on the effects of deferasirox on cardiac iron concentrations and dysfunction from large prospective randomised controlled studies - Deferasirox improves patient satisfaction and quality of life over desferrioxamine

	Desferrioxamine (Desferal®)	Deferiprone (Ferriprox®)	Deferasirox (Exjade®)
Long term efficacy	- lengthens survival	- no data on long-term outcomes (mortality and end organ damage)	- long term safety and efficacy of deferasirox is currently unknown.
Side effects	- common (>10%) side effects: local injection site disorder, arthralgia/myalgia - Growth retardation and bone changes may result from iron overload or excessive desferrioxamine dose :(1-10% in chelated patients given 60 mg/kg), esp. in children <3 year; but considerably less risk if ≤40 mg/kg. - Rare (0.01 to 0.1%): retinal abnormalities, vision loss, tinnitus and hearing loss - Very rare (≤0.01%): severe allergic reactions and thrombocytopenia	- common (≥10%) side effects: chromaturia (reddish brown urine), nausea, abdominal pain and vomiting. - -Arthropathy (>1 to ≤10%) ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability. - Serious adverse effects: in trials :agranulocytosis (1.1%) and neutropenia (4.9%) - reversible neurological disorders on chronic overdose has also been reported. - From 1999 to Nov 2006, 46 cases of agranulocytosis associated with deferiprone have been identified. Of these 9 were fatal, 4/9 fatal cases occurred since Sept 2005 where advice given in Product Information has not been followed. 5/9 fatal cases were prescribed for off label use. In all fatal cases weekly White Blood Cells monitoring were missing. - reported finding during clinical trials of liver fibrosis has not been confirmed.	- Common side effects: skin rash (7%), gastrointestinal symptoms (26%). - ↑ serum creatinine (33%), - Uncommon (≥0.1% to <1%) high-frequency hearing loss and early cataracts . - in post marketing surveillance, there have been reports of acute renal failure, some with a fatal outcome and cytopenias, including agranulocytosis, neutropenia and thrombocytopenia in the US where some of the patients died. Although most of these patients had pre-existing haematologic disorders that are frequently associated with bone marrow failure, a contributory role for deferasirox cannot be excluded.

	Desferrioxamine (Desferal®)	**Deferiprone (Ferriprox®)**	**Deferasirox (Exjade®)**
HADF classification	General	Special	Self Financed Item
Daily Cost $ 20kg-60kg body weight	$21.2-$169.4	$42-$168	$174.6 to $814.8
Current no. of pt in HA	403	233	19
Total annual cost to HA if all existing patients switched to Deferasirox	$25.7m to $119.9m	$14.8m to $69.3m	$1.21m to $5.7m

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