New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Deferasirox

Exjade (Novartis)

125 mg, 250 mg and 500 mg dispersible tablets

Approved indication: iron overload

Australian Medicines Handbook section 4.2

Patients who require frequent transfusions of blood, such as those with thalassaemia, are at risk of chronic accumulation of iron. This excess iron is deposited in the tissues such as the heart and liver resulting in damage and diminished function. To prevent organ failure these patients require the iron to be removed by chelating agents such as desferrioxamine. As desferrioxamine has to be given parenterally, oral chelating agents are being developed. Deferiprone was approved in Australia in 2003.

Deferasirox is another oral chelating agent. After absorption two molecules of deferasirox bind one atom of iron. The complex is then excreted in faeces. Deferasirox is metabolised and has an elimination half-life of 8–16 hours.

A short-term study of 24 adults with thalassaemia found that increasing doses of deferasirox increased iron excretion.[1] This led to a one-year study of 586 patients with a mean age of 17 years (range 2–53 years). They were randomised to take deferasirox or have subcutaneous desferrioxamine with the doses determined by the concentration of iron found on liver biopsy. (Patients randomised to desferrioxamine could remain on their previous dose.) Depending on the dose, both chelating agents reduced serum concentrations of ferritin. The mean reductions in liver iron concentration, when liver biopsies were repeated at the end of the study, were 2.4 mg/g with deferasirox and 2.9 mg/g with desferrioxamine. Overall 53% of the patients taking deferasirox achieved the target liver iron concentration compared with 66% of the patients given desferrioxamine.

In the main clinical trial serious adverse events such as infections affected approximately 9% of both groups. The most frequent adverse events associated with deferasirox were fever, headache, abdominal pain, nausea, vomiting and diarrhoea. In 11% of patients serum creatinine increased and 19% developed proteinuria. Renal function should therefore be monitored monthly. Monthly liver function tests are also recommended because there is a risk of drug-induced hepatitis. As deferasirox may cause cataracts and reduced hearing, annual eye examinations and hearing tests are advised.

Depending on how the results of the main trial are analysed, the efficacy of deferasirox may be inferior to that of desferrioxamine. In children aged 2–5 years it is only approved for use if desferrioxamine is ineffective or not tolerated.

There does not appear to be a published comparison of deferasirox and deferiprone. Deferasirox only needs to be taken once daily, but it is unknown if it has any other advantages.

T T manufacturer provided some data

Reference *

1. Nisbet-Brown E, Olivieri NF, Giardina PJ, Grady RW, Neufeld EJ, Sechaud R, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet 2003;361:1597-602.

Epoetin beta

Neorecormin (Roche)

Pre-filled syringes containing 1000 IU, 2000 IU, 3000 IU, 4000 IU, 5000 IU and 6000 IU per 0.3 mL, and 10 000 IU, 20 000 IU and 30 000 IU per 0.6 mL

Approved indication: specified anaemias

Australian Medicines Handbook section 7.6

Erythropoietin is a hormone which stimulates the production of red blood cells. A recombinant form, epoetin alfa, has been available for several years. Australian clinicians now have the option of prescribing recombinant epoetin beta, a form which has been available in Europe since 1990.

Like epoetin alfa, epoetin beta is genetically engineered using Chinese hamster ovary cells. Its protein sequence is indistinguishable from natural erythropoietin.

Following injection there is a dose-related response in the bone marrow. The dose is adjusted according to the packed cell volume or haemoglobin concentration. In the anaemia of chronic renal failure the regimen consists of a correction phase and then a maintenance phase.

Epoetin beta can be given by subcutaneous injection or by intravenous injection over two minutes. The bioavailability of the subcutaneous injection is less than half that of intravenous doses, but the half-life is longer (8–22 hours vs 4–12 hours) and lower doses can be used. In the correction phase of renal anaemia epoetin is given three times a week, but the subcutaneous injection can be given daily. It may be possible

during the maintenance phase to give a subcutaneous dose once every two weeks.

There have been several studies of epoetin beta for the anaemia of chronic renal failure. Most patients reach their target haematocrit after 12 weeks of treatment. Patients can successfully maintain their haematocrit with self-administered injections.[1] (This study used a pen injector which is not available in Australia.) While most of the patients will be on dialysis, epoetin beta can be used if patients with chronic renal insufficiency develop a symptomatic anaemia before starting dialysis.

Anaemia is common in patients with cancer particularly if they have been subjected to chemotherapy. In a placebo-controlled study of 349 patients with haematological malignancies, injecting epoetin beta subcutaneously three times a week for 16 weeks significantly reduced the need for blood transfusions. The patients' quality of life improved as their haemoglobin increased.[2] Another study of 241 patients with lymphoproliferative malignancies found that a once-weekly injection was as effective as three times a week.[3]

In addition to treating chemotherapy-induced anaemia in non-myeloid malignancies, epoetin beta, like epoetin alfa, is approved for increasing the yield of autologous blood donations, for example when people donate their own blood before undergoing surgery. Epoetin beta is also approved for preventing anaemia in premature babies.

As the packed cell volume increases the patient's blood pressure may rise. The risk of thrombosis may increase, particularly if there is a rise in platelet production. There is also a possibility that epoetin could stimulate tumour growth.

Iron studies and electrolytes should be regularly checked. Most patients will require iron supplements. Neutralising anti-erythropoietin antibodies can develop. If this results in red cell aplasia treatment must stop.

The pain of subcutaneous injections of epoetin beta has been compared with that of epoetin alfa. In a small study patients were injected with both products for four weeks. Pain scores were significantly lower with epoetin beta.[4] Another study compared epoetin beta with buffered formulations of epoetin alfa, and saline, by giving 60 patients four simultaneous injections. Epoetin beta was more acceptable than epoetin alfa and some patients felt it was no more painful than the saline injection.[5]

When indicated, epoetin beta will help to ameliorate the anaemia in most patients, but it may not improve long-term outcomes, at least in malignant disease. During a median follow-up of 27–28 months in 343 patients with lymphoproliferative malignancies, the median survival was 18 months with placebo and 17 months with epoetin beta.[6]

T T T manufacturer provided all requested information

References †

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4. Veys N, Vanholder R, Lameire N. Pain at the injection site of subcutaneously administered erythropoietin in maintenance hemodialysis patients: a comparison of two brands of erythropoietin. Am J Nephrol 1992;12:68-72.
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6. Osterborg A, Brandberg Y, Hedenus M. Impact of epoetin-β on survival of patients with lymphoproliferative malignancies: long-term follow up of a large randomized study. Br J Haematol 2005;129:206-9.

Rotavirus vaccine (Rotarix)

Rotarix (GlaxoSmithKline)

vials containing powder for reconstitution

Approved indication: prevention of rotavirus gastroenteritis

Australian Medicines Handbook section 20.1

Rotaviruses are a common cause of gastroenteritis in children. This can result in dehydration and, particularly in developing countries, death.

There are different strains of the virus. This vaccine has been developed from the common G1 serotype (89-12 strain). The production process results in a live attenuated vaccine which can be given orally (on the inside of the cheek).

A phase II trial in Singapore involved 2464 babies aged 11–17 weeks. They were given three different concentrations of the vaccine or a placebo. The seroconversion rate was 75–86% after a month. A second dose was then given and this resulted in 76–91% of the babies having antirotavirus antibodies one month later.[1]

A trial in South America gave three different concentrations of the vaccine to 1618 babies 6–12 weeks of age. Another group of 537 babies was given a placebo. Two months after the second dose of vaccine 61–65% of the babies had seroconverted. During the first year of life there were 1635 episodes of gastroenteritis but rotavirus was only isolated in 109 babies. Rotavirus gastroenteritis affected 3.58% (58/1618) of babies randomised to the vaccine group and 9.49% (51/537) of babies randomised

to the placebo group. Vaccine efficacy against rotavirus gastroenteritis was calculated to be 56–70%.[2]

Another South American trial gave the vaccine to 31 673 babies at the ages of two and four months. Compared to a control group of 31 552 given a placebo, the vaccinated babies had a significantly reduced rate of severe gastroenteritis. In the cohort of 20 169 babies followed until they were one year old, nine vaccinees needed hospital admission, compared with 59 of the placebo group. The vaccine efficacy against severe gastroenteritis was 85%.[3]

Adverse events which had a higher incidence with the vaccine than with placebo included irritability, flatulence, diarrhoea, reduced appetite and fever.

The vaccine can be given at the same time as other vaccines. Although it can be given with oral polio vaccine, a gap of two weeks is suggested. As viral antigen is excreted in the stools there is a potential for transmission to other people.

A different rotavirus vaccine marketed in the USA was withdrawn in 1999 after it was associated with intussusception. During the large South American study there were nine cases of intussusception following vaccination compared with 16 in the placebo group. Although the difference was not statistically significant, 56 deaths occurred after vaccination compared with 43 in the placebo group.[3]

The vaccine is most likely to be of benefit in communities with a high incidence of severe rotavirus gastroenteritis. Whether the multivalent vaccines under development will have greater effectiveness than this monovalent vaccine is currently uncertain.

T T manufacturer provided some data

References †

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3. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11-22.

Rotavirus vaccine (RotaTeq)

RotaTeq (Merck Sharp & Dohme)

tubes containing 2 mL suspension

Approved indication: prevention of rotavirus gastroenteritis

Australian Medicines Handbook section 20.1

Rotavirus is a leading cause of severe gastroenteritis in young children worldwide. Rotavirus-induced disease is responsible for the hospitalisation of approximately 10 000 Australian children each year. Between July 2004 and June 2005, the most prevalent serotypes in Australia were G1 (48.3%), G3 (36.7%) and G9 (6.9%), with G2 and G4 serotypes also causing some infections (less than 1%).[1] However, the prevalent serotype can change over time and in 2002–03, G9 was the dominant strain causing almost 75% of cases, with G1 responsible for only 11% of infections.[2]

This live oral pentavalent vaccine contains five types of rotavirus. The viral surface proteins correspond to human rotavirus serotypes G1, G2, G3, G4 and P[8]. The P[8] antigen was included in the vaccine to potentially provide protection against other G-serotypes that may contain P[8], for example serotype G9.

Safety and efficacy data for the vaccine were examined in a placebo-controlled trial of 68 038 babies. The vaccine was given to healthy infants with the first dose administered between 6 and 12 weeks of age then followed by two more doses at 4–10 week intervals. All infants had been immunised by the age of 32 weeks. Oral polio vaccine was not permitted to be given at the same time; however other childhood vaccines were allowed.[3]

Serum antibody responses were measured in a sub-group of 189 babies 14 days after the third dose. The seroconversion rates for neutralising antibody (specific to serotypes contained in the vaccine) and antirotavirus IgA were higher in the vaccine group compared to the placebo group. However, it is not known if these antibodies are responsible for protection against rotavirus gastroenteritis.

The number of hospitalisations or emergency department visits due to infections with G1–4 and G9 serotypes was evaluated. There were 383 cases in the 28 646 babies given the placebo compared to only 20 cases in the 28 488 babies given the vaccine. Depending on the serotype, the vaccine efficacy against hospitalisation or emergency department visits varied from 87.6% to 100%. Although these findings were statistically significant, the incidence of infections with some of the serotypes was very low.[3]

In an efficacy sub-group analysis, vaccine efficacy against G1–4 and G9 rotavirus gastroenteritis of 'any severity' was evaluated during the first rotavirus season. There were 318 cases of infection among the 2305 babies in the placebo group compared to only 83 cases in the 2207 vaccinees.[3]

There is an indication that the efficacy of this vaccine may decline in subsequent seasons since during the second rotavirus

season the efficacy dropped from 71.3% (first and second season) to 62.6%. Protection beyond a second rotavirus season was not evaluated in this trial.

A previous rotavirus vaccine, which was shown to be highly efficacious against rotavirus infection, was voluntarily withdrawn in 1999 because of an association with intussusception in babies after the first dose. In the trial of the new vaccine, all 68 038 babies were monitored for at least 42 days after each dose for serious adverse effects. Overall, there were 30 cases of intussusception – 12 of these occurred in the vaccine group and 18 in the placebo group. Only six cases occurred within 42 days of vaccination compared to five in the placebo group. There were ten cases of rectal bleeding in the vaccine group compared to three cases in the placebo group. The number of serious adverse events (fever, vomiting and diarrhoea) and deaths were similar in the vaccine and placebo groups. Dermatitis was more common among vaccine recipients.[3]

This vaccine can be given at the same time as other vaccines except oral polio vaccine.

It seems likely that this pentavalent vaccine will reduce hospitalisations due to prevalent rotavirus serotypes that cause gastroenteritis in Australia. It is not known if this vaccine will be more effective than the monovalent vaccine currently being marketed.

[T][T] manufacturer provided some data

References *

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The T-score ([T]) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

Answers to self-test questions

1. True
2. False
3. True
4. True
5. True
6. True
7. True
8. True
9. False

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