

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Arsenic trioxide

Phenasen (Phebra)

10 mL vials containing 10 mg/10 mL

Approved indication: acute promyelocytic leukaemia

Australian Medicines Handbook Appendix A

Acute promyelocytic leukaemia is a subtype of acute myeloid leukaemia. There is a translocation of chromosomes 15 and 17 resulting in the expression of abnormal proteins. It is currently treated with regimens containing all-*trans*-retinoic acid. The persistence of an abnormal transcript, promyelocytic leukaemia-retinoic acid receptor- α (PML-RAR α), after chemotherapy predicts relapse. Relapses can be managed with chemotherapy, but the toxicity is high so alternatives are needed.

The active ingredient in a traditional Chinese medicine used to treat leukaemia was found to be arsenic trioxide. Chinese researchers therefore tried a purified solution of arsenic trioxide in the treatment of relapsed acute promyelocytic leukaemia. The percentage of blast cells in the bone marrow was reduced to less than 5% in 14 of 15 patients. These complete responses were obtained after a median of 38 days treatment with arsenic trioxide.¹

An American study then tried arsenic trioxide in 12 patients with relapsed disease. Although one patient died the others all had a complete response after a median of 33 days. In eight patients PML-RAR α was no longer present after two courses of treatment.²

A multicentre study enrolled 40 patients during their first or second relapse. There was a complete response, confirmed by bone marrow examination in 34 patients. In 25 patients the PML-RAR α transcript was no longer present after treatment. Overall survival at 18 months was estimated to be 66%.³

The recommended regimen of arsenic trioxide for relapsed disease is a daily intravenous infusion until there is bone marrow remission. Three to six weeks after induction therapy is completed, 25 doses of arsenic trioxide are given in a consolidation regimen which can last for up to five weeks.

The infusion is given over 1–2 hours. Pharmacokinetic information is limited, but arsenic trioxide is thought to be metabolised in the liver and excreted in the urine.

As the clinical trials only involved small numbers of patients, safety data are limited. All patients will experience some drug-related adverse events. Common complaints are oedema, fever, fatigue, nausea, vomiting, diarrhoea and abdominal

pain. Hypokalaemia, hyperglycaemia and hypocalcaemia are also frequent. In the multicentre study of arsenic trioxide, 25% of the patients developed symptoms suggestive of acute promyelocytic leukaemia differentiation syndrome. This presents with fever, weight gain, dyspnoea, pulmonary infiltration and pleural or pericardial effusions. It requires urgent treatment with high doses of intravenous steroids. Arsenic prolongs the QT_c interval on the ECG so patients have an increased risk of arrhythmia. It is therefore important to monitor the patients for electrolyte abnormalities which may contribute to potentially fatal arrhythmias.

Arsenic is a carcinogen. It also suppresses the production of normal blood cells so blood counts and coagulation should be checked twice a week.

Patients with relapsed promyelocytic leukaemia are likely to respond to arsenic trioxide. If remission has not occurred within 60 days the patient is unlikely to respond. The published clinical trials have not compared arsenic trioxide with other approaches to treating relapsed disease. The optimum use of arsenic trioxide with other treatments needs further study to see if the high response rates translate into improved long-term survival.

T manufacturer provided only the product information

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Etoricoxib

Arcoxia (Merck Sharp & Dohme)

30 mg, 60 mg and 120 mg tablets

Approved indications: analgesia, gout, osteoarthritis

Australian Medicines Handbook section 15.1.1

Etoricoxib is a non-steroidal anti-inflammatory drug which mainly inhibits the cyclo-oxygenase-2 enzyme (see 'COX-2

inhibitors', *Aust Prescr* 2000;23:30–2). By reducing the synthesis of inflammatory mediators, etoricoxib can modify the pain response.

Acute gout presents with pain and inflammation. Etoricoxib has therefore been studied in the early treatment of acute gout in a double-blind trial involving 150 patients. The patients were randomised to take indomethacin 50 mg three times a day or a once-daily dose of etoricoxib 120 mg for eight days. Both drugs reduced pain and swelling with no significant differences in efficacy. Overall, there was no significant difference in adverse events, but etoricoxib caused fewer drug-related adverse effects.¹

Etoricoxib is also approved for use in primary dysmenorrhoea and postoperative dental pain. A single dose of 120 mg provides similar analgesia to ibuprofen 400 mg and naproxen 550 mg.

The early studies of etoricoxib in osteoarthritis used a dose of 60 mg daily. This dose was found to have the maximum efficacy in a six-week dose-ranging trial involving 617 patients with osteoarthritis of the knee.² In a 12-week study of 501 patients with osteoarthritis of the hip or knee, etoricoxib 60 mg reduced pain significantly more than placebo. Its efficacy was similar to that of naproxen 500 mg twice daily.³

Two longer-term studies also compared etoricoxib 60 mg daily with naproxen 500 mg twice daily. Almost 1000 patients were randomised to take etoricoxib, naproxen or a placebo for 12 weeks. This was followed by a 40-week comparison of etoricoxib and naproxen and then an 86-week extension study. The active drugs were significantly better than placebo in the first 12 weeks. After 52 weeks there was no significant difference between etoricoxib and naproxen. The reduction in pain was maintained over the whole 138 weeks of the studies.⁴

Following the withdrawal of rofecoxib in 2004, there has been increased concern about the adverse effects of COX-2 inhibitors. Although 60 mg is a more effective dose², the recommended dose of etoricoxib for osteoarthritis has been reduced to 30 mg daily. This dose was used in a trial which compared the drug with placebo or ibuprofen 800 mg three times daily for 12 weeks. The 528 patients in the study had osteoarthritis of the knee or hip. The active drugs had comparable efficacy, but were significantly better than placebo. Most of the benefit was achieved by the second week of treatment.⁵

Although COX-2 inhibitors were expected to have fewer serious gastrointestinal complications than other non-steroidal anti-inflammatory drugs, abdominal pain can be a reason for people stopping treatment with etoricoxib. After 40 weeks of treatment, 8.5% of the patients discontinued etoricoxib 60 mg because of drug-related adverse events (11.4% of the naproxen group discontinued). Common adverse effects included dyspepsia, epigastric discomfort, heartburn and hypertension.⁴ In the study of etoricoxib 30 mg, only 3.3% of the patients discontinued because of drug-related adverse events, compared with 9% of the ibuprofen group.⁵

Data from long-term comparisons of etoricoxib and diclofenac have been used to investigate cardiovascular and gastrointestinal safety. These studies involved more than 34 000 patients over the age of 50 years with rheumatoid arthritis or osteoarthritis. They took diclofenac 75 mg twice daily or 50 mg three times a day, or etoricoxib 60 mg or 90 mg daily. The mean duration of treatment was approximately 18 months. Thrombotic events, such as myocardial infarction and stroke, affected 468 of the patients taking diclofenac and 495 of those taking etoricoxib. This difference is not statistically significant.⁶ Upper gastrointestinal events occurred in 246 patients taking diclofenac and in 176 taking etoricoxib. This statistically significant advantage for etoricoxib was mainly accounted for by uncomplicated ulcers. Etoricoxib did not significantly reduce the rate of complications such as perforation and bleeding.⁷

Active peptic ulceration is a contraindication to etoricoxib as are vascular disease, heart failure and uncontrolled hypertension. Treatment should be stopped if hepatic dysfunction develops.

Etoricoxib is well absorbed and does not have to be taken with food. It is almost completely metabolised with most of the metabolites appearing in the urine. The long half-life enables once-daily dosing. Etoricoxib is contraindicated in patients with severe renal or hepatic impairment.

Caution is also advised if etoricoxib is considered for patients who are also taking drugs that are known to potentially interact with non-steroidal anti-inflammatory drugs. These drugs include ACE inhibitors, diuretics, oestrogens and lithium. Etoricoxib may also increase the effect of warfarin.

If etoricoxib is used for acute pain, the daily dose should not exceed 120 mg. This can only be used for a maximum of eight days.

Australian guidelines do not support long-term use of non-steroidal anti-inflammatory drugs or COX-2 inhibitors in osteoarthritis. Etoricoxib should be used at the lowest dose for the shortest possible time. If a patient's arthritic pain does not improve within a few weeks, the drug should be stopped. Although etoricoxib has been studied in rheumatoid arthritis, it is not approved for this condition.

T manufacturer provided only the product information

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Correction

New drugs, *Aust Prescr* 2009;32:112-5.
The brand name for eculizumab is Soliris.

The T-score (T) is explained in 'New drugs: transparency', *Aust Prescr* 2009;32:80-1.

- * 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 Medicines Agency (www.emea.europa.eu).

Answers to self-test questions

- | | | |
|----------|----------|----------|
| 1. False | 3. True | 5. False |
| 2. False | 4. False | 6. True |

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