

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.

Fampridine

Fampyra (Biogen)

10 mg modified release tablets

Approved indication: multiple sclerosis

Australian Medicines Handbook section 16.6

Fampridine is a potassium channel blocker indicated for symptomatic improvement of walking in adults with multiple sclerosis, including relapsing remitting, secondary progressive, progressive relapsing and primary progressive. Currently there are no other drugs for this indication.

Fampridine is thought to increase conduction in demyelinated nerves by inhibiting potassium channels. It can be used on its own or with other treatments for multiple sclerosis, including immunomodulatory drugs.

The efficacy of fampridine has been studied in two phase III trials.^{1,2} In the first trial, 301 patients with walking difficulties associated with multiple sclerosis were randomised to fampridine 10 mg twice daily or placebo, for 14 weeks. The primary outcome was based on changes in walking speed over 25 feet (7.6 m). A responder was defined as someone who consistently walked faster during treatment compared to baseline. In the fampridine group, 35% (78/224) of patients responded compared to only 8% (6/72) in the placebo group. The average increase in walking speed of people who responded to fampridine was 0.51 feet/second (approximately 15.5 cm/second) (25% faster).¹

These results were confirmed in a second similarly designed trial in which 43% (51/119) of patients responded to fampridine compared to only 9% (11/118) of patients to the placebo. On average, patients who responded to fampridine walked 24.7% faster.²

Urinary tract infection was a very common adverse event with fampridine. Neurological effects were common and included insomnia, balance disorder, dizziness, headache and asthenia. Falls and severe anxiety were also reported. In a trial of 206 patients, serious events were more common at higher doses (4% with placebo, 0% with 10 mg, 8% with 15 mg and 12% with 20 mg fampridine). One patient discontinued the 15 mg dose of fampridine because of nausea and dizziness and five patients discontinued the 20 mg dose – two patients had seizures, one developed abnormal coordination, one had chest discomfort and headache and one patient had blurred vision, chest discomfort, balance disorder, headache and paraesthesia.³

Seizures have also occurred postmarketing and fampridine is contraindicated in patients with a history of seizures. Because of this potential toxicity, patients should not take a double or extra dose when a dose is missed. Tablets should be taken whole and not crushed or chewed.

Following oral administration, peak concentrations of fampridine are reached after 3–4 hours. It is primarily excreted unchanged in the urine. The elimination half-life is normally 5.2–6.5 hours, but is prolonged in patients with renal impairment. Fampridine is therefore contraindicated in moderate to severe renal impairment. If renal function has not been assessed, creatinine clearance should be estimated before starting treatment. This is particularly important in the elderly. In patients with mild impairment, monitoring of renal function should be considered.

This drug has not been tested in pregnant and lactating women. As fampridine is lipophilic, it may be excreted in human milk.

Fampridine is the first drug to help improve walking in patients with multiple sclerosis. However in the trials, less than half of the patients (35–43%) consistently walked faster (increase of 15.5 cm/second) after taking fampridine. Doctors and their patients have to consider whether this potential benefit is worth the risk of seizures and other serious neurological adverse effects. The safety and efficacy of fampridine during an exacerbation of multiple sclerosis is not known as these patients were excluded from the trials. Fampridine should only be continued if the patient responds within eight weeks of treatment.

T manufacturer provided the product information

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Ferric carboxymaltose

Ferinject (Vifor Pharma)

2 mL solution containing 100 mg iron and 10 mL solution containing 500 mg iron for infusion

Approved indication: iron deficiency

Australian Medicines Handbook section 7.5.2

Intravenous ferric carboxymaltose is indicated for iron deficiency when oral preparations are ineffective or not tolerated. The molecule consists of an iron-hydroxide core chelated in a carbohydrate shell. After dilution and intravenous administration, it is found in the reticuloendothelial system of the liver, spleen and bone marrow and has a terminal half-life of 7–12 hours. Iron is incorporated into red blood cells 6–9 days after injection.

In a trial of 255 patients with chronic kidney disease and iron deficiency anaemia, ferric carboxymaltose given as an intravenous infusion (up to three doses totalling 2000 mg elemental iron over a month) was compared to oral ferrous sulfate (65 mg elemental iron three times a day). The majority of patients were not taking erythropoiesis-stimulating drugs. After eight weeks, more patients receiving ferric carboxymaltose had at least a 1 g/100 mL increase in haemoglobin than those receiving oral iron (60.4% vs 34.7% of patients). This was regardless of whether or not they were receiving erythropoiesis-stimulating drugs.¹

Ferric carboxymaltose has also been compared to iron sucrose in patients with chronic kidney disease who were on haemodialysis. All patients were receiving stable doses of an erythropoiesis-stimulating drug. Both treatments were given at a dose of 200 mg iron intravenously two to three times a week. After four weeks, haemoglobin levels had risen by at least 1 g/100 mL in 44.1% (52/118) of patients in the ferric carboxymaltose group and 35.3% (41/116) of those in the iron sucrose group. At the time of writing, this study was not published in full.

Ferric carboxymaltose has also been assessed in other conditions. In a trial of 200 patients with Crohn's disease or ulcerative colitis, treatment with up to three intravenous infusions of ferric carboxymaltose one week apart (up to 1000 mg iron a week) was found to be non-inferior to oral ferrous sulfate (100 mg iron twice a day). After 12 weeks, median haemoglobin concentrations had increased from 8.7 to 12.3 g/100 mL with ferric carboxymaltose and from 9.1 to 12.1 g/100 mL with oral iron.²

Ferric carboxymaltose was also effective in treating postpartum iron deficiency.³⁻⁵ In a six-week comparative trial of 291 women with anaemia (haemoglobin \leq 10 g/100 mL) after giving birth, 91.4% of women who received ferric carboxymaltose had haemoglobin concentrations greater than 12 g/100 mL. This was compared with 66.7% of women who received oral ferrous sulfate (65 mg iron three times a day).³

Generally, the most common adverse reactions to ferric carboxymaltose were headache, dizziness, nausea, abdominal pain, constipation, diarrhoea, rash and injection site reaction. These were reported by less than 10% of study participants. Decreased blood phosphorus and increased alanine aminotransferase also occurred in some patients. In patients with chronic kidney disease, peripheral oedema (6.1%), hyperkalaemia (4.1%) and urinary tract infection (3.4%) were the most common events.¹ In a safety cohort of 899 patients, there were five deaths. Causes included pulmonary tuberculosis, heart failure, peripartum cardiomyopathy leading to heart failure, myocardial infarction and cardiac arrest.

Transfer into human milk is negligible (\leq 1%) so breastfeeding is not a contraindication. In a safety analysis of 229 breastfed infants whose mothers were receiving ferric carboxymaltose, adverse reactions included erythema (5 babies), constipation (3 babies), diarrhoea (3 babies), nasopharyngitis (2 babies), pallor and flatulence (2 babies), abdominal pain (1 baby) and upper respiratory tract infection (1 baby).

This drug is contraindicated for anaemia not caused by iron deficiency, or if there is evidence of iron overload or disturbances of iron use. It should also not be used in the first trimester of pregnancy as fetal abnormalities have been observed in preclinical studies, and caution is urged in the second and third trimesters. In patients with hepatic impairment, ferric carboxymaltose should only be used after careful assessment and monitoring.

Anaphylaxis has occurred after intravenous injections of iron preparations so resuscitation facilities should be available during administration of ferric carboxymaltose.

The cumulative dose of ferric carboxymaltose required to restore iron levels should be individually calculated for each patient. As there is a risk of iron overload, patients should have their red cell indices and serum ferritin monitored regularly.

Evidence from the trials suggests that ferric carboxymaltose is an effective alternative for treating iron deficiency when oral iron is not an option. However, it is not clear if it will have advantages over other parenteral iron formulations such as iron sucrose.

T T T manufacturer provided clinical evaluation

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Palonosetron hydrochloride

Aloxi (Specialised Therapeutics)

vials containing 250 microgram/5 mL

Approved indication: prevention of nausea and vomiting

Australian Medicines Handbook section 12.3.2

Patients having cytotoxic chemotherapy are likely to develop severe nausea and vomiting. To try and prevent these adverse reactions patients are given antiemetic drugs. These include the serotonin (5HT₃) receptor antagonists dolasetron, granisetron, ondansetron and tropisetron.

Like the other members of the class palonosetron has a high affinity for the 5HT₃ receptor. Blocking this receptor reduces the response to the emetogenic stimulus induced by cytotoxic drugs.

To prevent the nausea and vomiting, palonosetron is given intravenously 30 minutes before chemotherapy. Plasma concentrations decline rapidly, but there is a long elimination half-life (mean 40 hours). Palonosetron is metabolised by several enzymes including cytochrome P450 2D6, but 40% of the dose is excreted unchanged in the urine. No dosage reductions are recommended for patients with hepatic or renal impairment.

The approved indication for palonosetron was mainly supported by two trials in patients having moderately emetogenic chemotherapy^{1,2} and one trial in patients having highly emetogenic chemotherapy.³

In the highly emetogenic study, 673 patients were randomised to receive different doses of palonosetron or a single dose of ondansetron. After 24 hours, 57% of the patients given ondansetron had experienced no vomiting or had not needed rescue medication. Among the patients given 250 microgram of palonosetron, 59% had a complete response.³

Ondansetron was also included in a study of moderately emetogenic chemotherapy involving 570 patients. There was

a complete response in 69% of the patients given ondansetron and in 81% of those given 250 microgram of palonosetron. This difference was statistically significant.¹

The other study of moderately emetogenic chemotherapy randomised 592 patients to take dolasetron or one of two doses of palonosetron. There was a complete response in 53% of the patients given dolasetron and in 63% of those given 250 microgram of palonosetron.²

The pattern and frequency of adverse reactions to palonosetron was similar to that of ondansetron and dolasetron. Headache and gastrointestinal symptoms, such as constipation, were the most frequently reported problems. Although palonosetron did not cause extensive QT prolongation in the trials, caution is advised when giving the drug to patients who are at risk of QT prolongation.

The trials show that palonosetron is not inferior to other 5HT₃ antagonists for the prevention of acute vomiting. The longer half-life may help in reducing the incidence of delayed nausea and vomiting,⁴ but the safety and efficacy of repeated dosing has not been evaluated.

T manufacturer provided the product information

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Vinflunine

Javlor (Pierre Fabre Medicament)

vials containing 50 mg/2 mL, 100 mg/4 mL or 250 mg/10 mL

Approved indication: bladder cancer

Australian Medicines Handbook section 14.1.8

Vinflunine is indicated for advanced or metastatic transitional cell carcinoma of the urothelial tract. It is intended as a second-line treatment for patients whose disease has progressed despite platinum-containing therapy. The median survival of these patients is four months and currently treatment focuses on best supportive care.

Vinflunine is a vinca alkaloid. Like other drugs in this class, it works by binding to tubulin and inhibiting its polymerisation into microtubules. This ultimately leads to mitotic arrest and apoptosis of the cell.

In early phase II trials, patients who had progressing or recurring disease after treatment with a platinum-containing regimen were given intravenous vinflunine 320 mg/m² every three weeks. Of the 202 patients treated, 31 (15%) had a partial response and 89 (44%) had stable disease. The median progression-free survival was 2.8–3 months and overall survival was 6.6–8.2 months.^{1,2}

In a larger phase III comparative trial, 370 patients were randomised to receive best supportive care with or without vinflunine (320 mg/m² every three weeks). Although the median survival was longer for patients receiving vinflunine compared to those receiving supportive care alone (6.9 months vs 4.6 months), the difference was not statistically significant ($p=0.287$). However, a *post hoc* analysis suggested a possible treatment effect ($p=0.04$). Significantly more people responded to vinflunine than to supportive care alone – 8.6% vs 0% had a partial response and 46.5% vs 27.1% had stable disease. Also, the median duration of disease control was significantly longer for vinflunine than for supportive care alone (5.7 vs 4.2 months), as was progression-free survival (3 vs 1.5 months). The median duration of treatment with vinflunine was 9.5 weeks. This was similar in the control group.³

Myelosuppression is a considerable problem with vinflunine. Approximately half of the 450 patients in the trials developed severe (grades 3–4) neutropenia or leucopenia. Anaemia and thrombocytopenia were also common but, in general, less severe. Infections were frequent and seven patients died from an infection that was a complication of neutropenia. Recent or current infection is a contraindication to vinflunine use. Complete blood counts should be measured before each infusion and the dose may need to be reduced or stopped if the patient has signs of toxicity.

Gastrointestinal symptoms are frequent with vinflunine. Severe constipation (15.3%) and ileus (2.2%) occurred in some patients

and dose reduction was required. Alopecia (28.7%) and peripheral sensory neuropathy (9.8%) were also frequently reported.

Cardiovascular effects have occurred with vinflunine and it should be used with caution in patients with a pre-existing heart condition. One patient died of myocardial infarction and another of cardiopulmonary arrest. Vinflunine may prolong the QT interval and concomitant use of drugs that prolong the QT interval should be avoided.

Vinflunine should be given as an intravenous infusion. Accidental intrathecal use of this class of drug has been fatal. After infusion, vinflunine is extensively distributed in the tissues. It is metabolised by cytochrome P450 3A4 and excreted in the faeces and urine. The dose of vinflunine should be reduced in patients aged 75 and over, and in those with impaired liver (mild to moderate) or kidney function (moderate to severe). Vinflunine is not recommended in severe hepatic impairment. Concomitant use of drugs that inhibit or induce CYP 3A4 should be avoided.

Although vinflunine is indicated for second-line treatment of advanced bladder cancer, patients and their doctors have to consider whether the potential modest increase in life expectancy is worth the risk of developing severe adverse effects. A review of vinflunine from a French drug bulletin concluded that in practice 'it is better to focus on individually tailored palliative care'.⁴

T manufacturer provided the AusPAR and the product information

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The T-score (**T**) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

- * 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.ema.europa.eu).
- A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

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