# 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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

## Darbepoetin alfa

Aranesp (Amgen)

prefilled syringes containing 10 microgram/0.4 mL, 20 microgram/0.5 mL, 30 microgram/0.3 mL, 40 microgram/0.4 mL, 50 microgram/0.5 mL, 60 microgram/0.3 mL and 100 microgram/0.5 mL

Approved indication: anaemia of chronic renal failure

Australian Medicines Handbook Section 7.5

In chronic renal failure erythropoiesis is reduced leading to a normochromic, normocytic anaemia. This can be treated by giving the patient recombinant erythropoietin to stimulate red cell production.

Although there are genetically engineered differences in its structure, darbepoetin can be used as an alternative to erythropoietin. The structural differences give darbepoetin a half-life three times longer than that of erythropoietin. After intravenous injection the half-life ranges from 12 to 40 hours and ranges from 27 to 89 hours after subcutaneous injection. Patients therefore need less frequent injections if they use darbepoetin instead of erythropoietin. A weekly injection should raise the haemoglobin by at least 10 g/L in four weeks, if the patient has adequate stores of iron. The product information explains how to calculate the dose of darbepoetin when switching a patient from erythropoietin.

In clinical trials darbepoetin and erythropoietin have had similar efficacy in the correction of anaemia. Both drugs are also effective at maintaining the haemoglobin concentration.

The adverse effects of darbepoetin resemble those of erythropoietin. Patients find the subcutaneous injection of darbepoetin more painful, but when given intravenously it causes less thrombosis of the vein than erythropoietin. Other adverse events include hypertension and myalgia. Uncontrolled hypertension is a contraindication to darbepoetin. So far there have been no reports of serious allergic reactions or patients developing antibodies to darbepoetin.

## Etanercept

Enbrel (Wyeth)

vials containing 25 mg

Approved indication: rheumatoid arthritis

Australian Medicines Handbook Section 15.2.2

The treatment of rheumatoid arthritis now involves the early use of disease-modifying antirheumatic drugs. Despite early intervention some patients will continue to have joint inflammation. Researchers have therefore been investigating how to control the cytokines involved in the inflammatory process.

Tumour necrosis factor is a cytokine found in the synovium. It stimulates cell proliferation and the production of inflammatory mediators. Etanercept blocks this action by binding to the receptors for tumour necrosis factor.

The etanercept molecule is a human tumour necrosis factor receptor fusion protein. It is produced by recombinant DNA technology.

Patients have to inject etanercept twice a week. After subcutaneous injection etanercept is slowly absorbed. It has a half-life of 70 hours, but the mechanism of elimination is unknown. There have been no pharmacokinetic studies to examine the effect of renal or hepatic impairment.

A double-blind placebo-controlled study enrolled 234 patients who had failed to respond to a disease-modifying antirheumatic drug. After six months of treatment 59% of the patients given etanercept had a 20% improvement in their symptoms and signs. In the placebo group only 11% had a similar response.

Another study investigated adding etanercept to methotrexate therapy. After 24 weeks 71% of the 59 patients taking the two drugs had at least a 20% improvement in their symptoms and signs. This was significantly greater than the response in the 30 patients taking methotrexate and placebo even though 27% of this group also improved.[1]

During the clinical trials etanercept was well tolerated, but there are post-marketing reports of serious adverse events. By inhibiting tumour necrosis factors etanercept may reduce the body's defences against infections and tumours. There were 22 serious infections and seven malignancies in 745 patients taking etanercept. Some patients with sepsis have died, so etanercept should be stopped if a serious infection develops. Extra caution is needed if etanercept is prescribed for patients who may have an increased risk of infection, for example patients with diabetes. Patients can develop autoantibodies, but no lupus-like reactions have been reported.

A common problem for patients is a reaction at the injection site. These reactions may be swelling, pain or itching and can last for several days. It is important that patients who are going to self-administer etanercept are instructed in how to prepare the injection. Other frequent adverse events include headache and upper respiratory infections.

When a patient stops injecting etanercept their arthritis usually returns within a month. At present, there is limited information about the long-term continuous use of etanercept. This therapy is likely to be very expensive and there is currently no method of predicting which patients will benefit from etanercept. It should be reserved for patients who have not responded to other drugs.

REFERENCE

1. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.

## Laureth-9

Aethoxysklerol (Smith & Nephew)

2 mL ampoules containing 0.5%, 1% and 3%

Approved indication: varicose veins

Australian Medicines Handbook Section 6.7.1

Laureth-9, also known as polidocanol, is an emulsifying agent. When it is injected into a vessel it damages the endothelium resulting in a thrombosis. In combination with compression bandaging, laureth-9 can be used to treat varicose veins in the legs. As laureth-9 has some anaesthetic effects this scelerotherapy is relatively painless.

In an Australian study laureth-9 was used to treat varicose veins, telangiectasia and venule ectasia. After treating 16 804 limbs, the investigators' subjective impressions were that the results were superior to sclerotherapy with hypertonic saline or sodium tetradecyl sulfate. Adverse reactions were also considered to be less severe.[1]

The adverse effects of laureth-9 include phlebitis, tissue necrosis at the injection site and pigmentation in the sclerosed area. Some patients will develop allergic reactions so the practitioner should be equipped to treat anaphylaxis. If the injection has been into paravenous tissue, an injection of 1% procaine hydrochloride or normal saline, and if possible hyaluronidase, is recommended.

Larger veins require a higher concentration of laureth-9. Usually only 0.1–0.3 mL needs to be injected into smaller veins. Very fine needles should be used. After the injection a compression bandage is applied and the patient should walk around for 30 minutes. For medium sized veins the bandage is worn for 4–6 weeks. Repeated treatment may be required, but the veins may still not disappear completely in all patients.

REFERENCE

1. Conrad P, Malouf GM, Stacey MC. The Australian polidocanol (aethoxysklerol) study. Results at 2 years. Dermatol Surg 1995;21:334-6.

## Oxcarbazepine

Trileptal (Novartis)

300 mg film-coated tablets

Approved indication: epilepsy

Australian Medicines Handbook Section 16.1.3

Carbamazepine is efficacious in the treatment of partial seizures and generalised tonic-clonic seizures. Its effectiveness is limited by its toxicity and interactions. Oxcarbazepine is an analogue of carbamazepine which has been developed to overcome some of these problems. It has been available in some parts of Europe for several years.

Oxcarbazepine is taken twice a day. The dose can be increased at weekly intervals. This is a more rapid titration than with carbamazepine. Each dose is well absorbed and then converted to an active metabolite. This metabolite has a half-life of nine hours, whereas the half-life of oxcarbazepine is two hours. Less than 1% of the dose is eliminated unchanged with most of the metabolites being excreted in the urine. Renal clearance is increased in children and reduced in the elderly.

Like other recently marketed antiepileptic drugs[1], oxcarbazepine has been used as an adjunct to other treatments. It is efficacious in adults and children with partial seizures uncontrolled by other drugs.[2]

Oxcarbazepine has also been studied as monotherapy. It is more effective than placebo at controlling partial seizures. In patients with previously untreated partial or generalised tonic-clonic seizures, oxcarbazepine was as efficacious as sodium valproate and phenytoin.

Fatigue, dizziness, drowsiness, nausea and vomiting are common adverse reactions. Hyponatraemia can develop particularly during the first three months of treatment. The product information recommends that patients with renal problems, or those taking medications such as diuretics or non-steroidal anti-inflammatory drugs, should have their serum sodium measured frequently at the start of therapy.

If patients have a history of hypersensitivity reactions to carbamazepine, there is a 25–30% chance that they will react to oxcarbazepine.

Unlike carbamazepine, the metabolism of oxcarbazepine is not affected by drugs, such as erythromycin, which inhibit CYP3A4. Oxcarbazepine can inhibit CYP2C19 so there is a potential for interactions with phenytoin. There are also interactions with calcium channel blockers and oral contraceptives because oxcarbazepine induces CYP3A4 and CYP3A5.

Although oxcarbazepine may have some advantages over carbamazepine, there is less information about its long-term safety. Oxcarbazepine is also likely to be more expensive.

REFERENCES

1. Kilpatrick C. New antiepileptic drugs. Aust Prescr 1999;22:61-3.
2. Castillo S, Schmidt DB, White S. Oxcarbazepine add-on for drug-resistant partial epilepsy (Cochrane Review). In: The Cochrane Library, 4, 2001. Oxford: Update Software.

## Pioglitazone hydrochloride

Actos (Eli Lilly Australia)

15 mg, 30 mg and 45 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook Section 10.1

Many patients with type 2 diabetes cannot control their glucose concentrations with diet alone. These patients have insulin resistance which may benefit from treatment with a thiazolidinedione.

The thiazolidinediones act on the peroxisome proliferator-activated receptor.[1] This leads to an increased sensitivity of muscle and adipose tissue to insulin. The drugs also reduce gluconeogenesis in the liver.

Although there are few published studies, pioglitazone has been approved for use as monotherapy or in combination with other drugs, including insulin, for the treatment of type 2

diabetes. This approval appears to be based on clinical trials lasting 16 or 26 weeks.

The studies using pioglitazone as monotherapy found that it had a significantly greater effect, than a placebo, on fasting blood glucose and $HbA_{1C}$. In combination with a sulfonylurea, or metformin, pioglitazone will produce greater reductions in fasting blood glucose and $HbA_{1C}$ than a placebo. Similar effects were seen when pioglitazone was given to patients who were already taking insulin for their type 2 diabetes.

Patients taking insulin should start with a lower dose (15 mg) of pioglitazone. The recommended dose when pioglitazone is used in combination with other drugs is 30 mg.

Pioglitazone can be given once a day. Although it has a half-life of 5–6 hours, pioglitazone has an active metabolite which has a half-life of 16–23 hours.

Following the serious adverse reactions which lead to the withdrawal of troglitazone, there is concern about the hepatotoxicity of the thiazolidinediones. Similar adverse effects were not reported during the trials of pioglitazone, but liver function must be monitored regularly. During the first year of treatment the liver function should be tested every eight weeks.

The thiazolidinediones also alter lipid metabolism. This may include an increase in low density lipoprotein. In animal studies there has been cardiac hypertrophy. Although echocardiographic studies have not shown this effect in humans, the studies have excluded patients with heart disease.

More common adverse effects include oedema, headache and myalgia. Less than 4% of the patients in the clinical trials withdrew because of adverse effects.

Although cytochrome P450 3A4 is involved in the metabolism of pioglitazone there are no studies of interactions with other drugs metabolised by this enzyme. Pioglitazone may reduce the effectiveness of oral contraception. While it does not alter the steady-state pharmacokinetics of metformin and glipizide caution is needed when combining drugs such as these with pioglitazone. The combination with an oral hypoglycaemic drug or insulin increases the risk of hypoglycaemia.

To ascertain the role of pioglitazone there is a need for comparative studies to be published. There is currently not enough evidence to suggest that pioglitazone should become the first-line treatment after diet fails to control a patient's blood glucose.

REFERENCE

1. Schoonjans K, Auwerx J. Thiazolidinediones: an update. Lancet 2000;355:1008-10.

## Sibutramine hydrochloride

Reductil (Abbott)

10 mg and 15 mg capsules

Approved indication: obesity

Australian Medicines Handbook Section 12.10

Drugs are not the first-line treatment for people who are overweight (see 'Obesity and its management', Aust Prescr 1999;22:12-6). Sibutramine can be considered for obese patients who are unable to reduce their weight despite changing their diet and taking more exercise. It should only be considered if the patient's body mass index is at least 30 $kg/m^2$ (27 $kg/m^2$ if there are other risk factors such as hypertension or diabetes).

Although depression is not an approved indication, sibutramine is a serotonin reuptake inhibitor. It also inhibits the reuptake of noradrenaline and dopamine. Sibutramine is structurally related to amphetamine and is mainly thought to act through its amine metabolites.

After its rapid absorption sibutramine undergoes extensive first-pass hepatic metabolism. As cytochrome P450 3A4 is involved in the metabolism there is a potential for interactions with drugs which induce (e.g. phenytoin) or inhibit (e.g. erythromycin) this enzyme. The active metabolites have a half-life of 14-16 hours and are also eliminated by metabolism.

Patients start treatment with a daily dose of 10 mg. If they have lost less than 2 kg after four weeks, the dose can be increased to 15 mg daily. Treatment should stop if the patient has not lost 5% of their weight after three months. Weight loss in patients with diabetes is slower so they can have a six month trial of treatment.

The maximum weight loss usually occurs after six months treatment. Approximately 60% of the patients who lose 2 kg in the first month of treatment will lose 5% or more of their body weight by six months.

In a double-blind trial 485 obese people were given dietary advice and took either sibutramine or a placebo. After a year 39% of the patients taking 10 mg and 57% of the patients taking 15 mg had lost at least 5% of their body weight, compared with only 20% of those who took a placebo.[1] Another study showed the importance of lifestyle modification. Women who just took sibutramine only lost 4.1% of their body weight after a year, whereas those who also modified their lifestyle lost 10.8% of their body weight. The weight loss was even greater if they also followed a diet.[2]

Sibutramine increases heart rate and blood pressure. Patients should therefore have their pulse and blood pressure checked at least every two weeks in the first three months of treatment and then at least once every three months. A sustained rise in heart rate of 10 beats/minute or a 10 mmHg increase in blood pressure are indications for stopping treatment. A history of coronary or cerebrovascular disease contraindicates sibutramine. Frequent adverse effects include loss of appetite, dry mouth, constipation and insomnia.

The options for the drug treatment of obesity are limited. Sibutramine does not seem to be a major advance. Although it produces statistically significant weight loss the clinical benefit of losing a few kilograms is questionable. In the year-long study the mean weight loss with 10 mg sibutramine was 4.4 kg, only slightly greater than the weight loss of 1.6 kg in the placebo group.[1] Although some patients who have responded to six months treatment have continued to take sibutramine for up to two years they do not continue to lose weight. The achieved weight loss is largely maintained while patients continue to take the drug, but they start to regain weight as soon as they stop.[3] There is no information on the long-term effects of sibutramine on the mortality and morbidity of obesity.

REFERENCES

1. Smith IG, Goulder MA. Randomized placebo-controlled trial of long-term treatment with sibutramine in mild to moderate obesity. J Fam Pract 2001;50:505-12.
2. Wadden TA, Berkowitz RI, Sarwer DB, Prus-Wisniewski R, Steinberg C. Benefits of lifestyle modification in the pharmacologic treatment of obesity. Arch Intern Med 2001;161:218-27.
3. James WPT, Astrup A, Finer N, Hilsted J, Kopelman P, Rössner S, et al. Effect of sibutramine on weight maintenance after weight loss: a randomised trial. STORM Study Group. Lancet 2000;356:2119-25.

## Zoledronic acid

Zometa (Novartis)

vials containing 4 mg as dry powder

Approved indication: tumour-induced hypercalcaemia

Australian Medicines Handbook Section 10.4.2

Zoledronic acid is a bisphosphonate with a hydroxyl group and an imidazole side chain. This structure makes zoledronate a potent inhibitor of osteoclastic bone resorption. (See 'Bisphosphonates – mechanisms of action' Aust Prescr 2000;23:130-2).

Bone resorption is an important cause of the hypercalcaemia seen in some cancers. Rehydration and bisphosphonates such as clodronate and pamidronate can therefore be used to return calcium concentrations to normal. As zoledronic acid is a more potent bisphosphonate it may give improved results.

Clinical trials have compared a five-minute infusion of zoledronic acid with a two-hour infusion of pamidronate. Ten days after the infusion approximately 88% of patients with tumour-induced hypercalcaemia had responded to zoledronic acid while 70% had responded to pamidronate.

The median time for patients to relapse is significantly longer after zoledronic acid (30 days versus 17 days for pamidronate). This may be related to its long half-life of 167 hours. The drug is excreted unchanged in the urine so it is not recommended for patients with severe renal impairment.

In patients with cancer adverse events are common. Adverse reactions that have been attributed to zoledronic acid include nausea, fever and itching. Hypocalcaemia will occur in 6% of patients. If this is symptomatic the patient may need to be given calcium gluconate. Renal function should be monitored as it can be impaired by bisphosphonates. This risk may be reduced by giving the infusion over 15 minutes.

Zoledronic acid is an effective treatment, but it is less effective once the patient has relapsed. Retreatment with a higher dose has a response rate of 52%. Patients who are refractory to the first dose should not be retreated for at least a week. As zoledronic acid also has some antitumour effects it is being studied in patients with bony metastases or myeloma.

## Answers to self-test questions

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

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