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Conflict of interest: none declared

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.

Degarelix

Firmagon (Ferring)

vials containing 80 mg and 120 mg as powder for reconstitution

Approved indication: prostate cancer

Australian Medicines Handbook section 14.3

Androgen deprivation is one approach to the treatment of prostate cancer. This can be achieved by using agonists of gonadotrophin releasing hormone such as goserelin and leuprorelin. Although these drugs cause an initial surge in testosterone, long-term use leads to decreased production.

Degarelix reduces testosterone production by antagonising gonadotrophin releasing hormone. By blocking the pituitary receptors, degarelix cuts testosterone concentrations within a few days, without the surge seen with gonadotrophin releasing hormone agonists.

In a dose-ranging study, 127 patients were randomised to take a starting dose of degarelix followed by monthly maintenance doses. Within three days the testosterone concentration had fallen into the target range in 89% of the men. Low levels were maintained in most of the 87 men who completed the one-year study. Prostate specific antigen was also reduced.[1]

Degarelix has to be given by subcutaneous injection into the abdomen. A depot is thought to form at the injection site so that the drug is slowly released. The half-life of the maintenance dose is estimated to be 28 days. Most of the dose is metabolised by hydrolysis and excreted in the faeces. The dose does not have to be adjusted in patients with mild to moderate renal or hepatic impairment.

Degarelix has been compared with intramuscular leuprorelin in a 12-month study. The 610 men in the study had prostate cancers ranging from localised to metastatic. Those who were randomised to take degarelix were given 240 mg followed by monthly maintenance doses of 80 mg or 160 mg. The desired testosterone concentration was achieved by 97–98% of the degarelix groups and 96% of the leuprorelin group.

The reduction in testosterone was more rapid in the degarelix groups. A similar pattern was seen with the reduction in prostate specific antigen.[2]

Adverse effects are common with degarelix. In the comparative study, 40% of patients had injection-site reactions with degarelix. Less than 1% of the leuprorelin group had injection-site reactions. Other adverse effects reported in the trial included flushing, weight gain and altered liver function. Adverse events resulted in approximately 7–9% of the degarelix group and 6% of the leuprorelin group discontinuing treatment.[2] During treatment with degarelix the QTc interval on the ECG can be prolonged and some patients will develop anaemia. Some patients develop antibodies to degarelix although it is yet unclear whether this affects long-term efficacy. Although androgen deprivation has metabolic effects, lipids other than cholesterol, and glucose were not studied. Hypercholesterolaemia occurred in 5% of patients given degarelix.[2]

It appears that an antagonist of gonadotrophin releasing hormone is as effective as an agonist in reducing testosterone concentrations. While at first the reduction is more rapid than with leuprorelin, after about a month there is no significant difference between treatments. Further study will be needed to see the effect of degarelix on survival and whether it has any role in patients who have not responded to a gonadotrophin releasing hormone agonist.

T T T manufacturer provided clinical evaluation

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Denosumab

Prolia (Amgen)

vials containing 60 mg/mL solution for injection

Approved indication: osteoporosis

Australian Medicines Handbook section 10.3.3

Denosumab is a humanised monoclonal antibody approved for the treatment of osteoporosis in postmenopausal women. This antibody works by binding RANKL (receptor activator of nuclear factor-κβ ligand) and blocking the interaction with its receptor on the surface of osteoclasts. This inhibits the development and activity of osteoclasts and leads to decreased bone resorption and increased bone density.

Following a subcutaneous dose of denosumab 60 mg, maximum serum concentrations are typically reached one to four weeks later. Denosumab has a half-life of 25–30 days. It is not eliminated via hepatic metabolism and dose adjustment is not needed in patients with renal impairment.

The approval of denosumab for osteoporosis is mainly based on a large phase III randomised trial which enrolled 7868 women aged 60–90 years. These women had to have a bone mineral density T score of less than –2.5 at the lumbar spine or total hip before being randomised to receive subcutaneous denosumab 60 mg or placebo every six months. After three years of treatment, the incidence of new vertebral fractures (measured radiolographically) was significantly lower for denosumab than for placebo (2.3% vs 7.2%). Denosumab also significantly reduced the cumulative incidence of hip fractures (0.7% with denosumab vs 1.2% with placebo) and nonvertebral fractures (6.5% with denosumab vs 8% with placebo). Over the same time period, denosumab was associated with a relative increase in bone mineral density at the lumbar spine (9.2%) and hip (6%) in a subset of 441 women. Markers of bone turnover (serum C-telopeptide) and bone formation (serum procollagen type I N-terminal propeptide) were also decreased in women receiving denosumab.[1] Although the efficacy data from this trial looks promising, a meta-analysis of three randomised controlled trials found that denosumab was not associated with a significant reduction in fracture risk in postmenopausal women.[2]

The efficacy of denosumab in reducing fractures has not been compared to other treatments for osteoporosis. However, a phase III trial looking at bone mineral density compared denosumab (six-month dose) to alendronate (70 mg orally each week) in women with low bone mass (T score ≤ –2.0). After 12 months, bone mineral density of the hip had increased more with denosumab than with alendronate (3.5% vs 2.6%). Although this was statistically significant, the clinical significance of this change is unclear. This increase was associated with a more pronounced decrease in markers for bone turnover in the denosumab group.[3]

In the placebo-controlled trial, eczema and flatulence were more common with denosumab than placebo (3% vs 1.7% and 2.2% vs 1.4%). Cellulitis, a serious adverse event, was also more frequent in women receiving denosumab (12/3886) compared to those receiving placebo (1/3876).[1] This may not be so surprising as RANKL is expressed on immune cells and its inhibition could make people more susceptible to infections. When a larger safety cohort (over 8000 people) was analysed, serious infections were more common with denosumab than placebo (3.4% vs 2.8%) and included abdominal, ear and urinary tract infections as well as cellulitis. Endocarditis, infected arthritis and skin ulcers were also more frequently reported. Malignancies are also a concern with denosumab and cancers were slightly more common with denosumab than with placebo (7.8% vs 7.1%). These risks should be considered when prescribing denosumab and patients should be informed of them.

In the safety cohort, serious pancreatitis occurred more commonly with denosumab than with placebo (9 cases vs 1 case). This proved fatal in two people.

Low osteoclast and osteoblast counts have been observed with denosumab. This could potentially delay healing of fractures. Transient hypocalcaemia can occur with denosumab and is a contraindication to treatment. Calcium and vitamin D supplementation is recommended for all patients. Neutralising antibodies were not found in women who received denosumab.

Denosumab seemed to reduce fractures in postmenopausal women with low bone density in a large placebo-controlled trial. However, because of lack of head-to-head trials it is not known how this efficacy compares with current treatments for osteoporosis. Women may prefer the six-monthly dosing of denosumab but will need to consider its increased risks of infections and malignancies. Postmarketing surveillance for these adverse effects is needed.

T T T manufacturer provided clinical evaluation

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Eletriptan hydrochloride

Relpax (Pfizer)

40 mg and 80 mg film-coated tablets

Approved indication: migraine

Australian Medicines Handbook section 16.3.2

Naratriptan, sumatriptan and zolmitriptan are already available for the treatment of migraine. They are now joined by eletriptan, another serotonin (5-HT_1) agonist, which was originally approved for use in Australia in 2000.

Compared with sumatriptan, eletriptan is more lipophilic and has a higher bioavailability. Although at least 80% of the dose is rapidly absorbed, the absolute bioavailability of eletriptan is 50%. The maximum concentration is reached within two hours, but there is a delay if the drug is taken during a migraine attack.

Eletriptan acts on the 5-HT_{1B} receptors which control the constriction of intracranial blood vessels. It also acts on the 5-HT_{1D} and 5-HT_{1F} receptors of the trigeminal nerve.

The half-life of eletriptan is four hours. It is metabolised by the cytochrome P450 system. As CYP3A4 is involved, inhibitors of this enzyme, such as erythromycin or ketoconazole, will increase the plasma concentrations of eletriptan. Eletriptan is therefore contraindicated within 48 hours of treatment with a potent CYP3A4 inhibitor. It is also contraindicated in patients with severe hepatic impairment.

Although eletriptan is mainly eliminated by non-renal clearance, caution is still needed when prescribing for patients with renal impairment. This is because the increase in blood pressure caused by eletriptan is amplified in these patients. The vasoconstrictive effect of eletriptan contraindicates its use in patients with uncontrolled hypertension, coronary heart disease, cerebrovascular disease and peripheral vascular disease. Patients who are at risk of cardiac disease are recommended to have a cardiovascular evaluation before starting treatment with eletriptan. The drug should not be taken at the same time as an ergot alkaloid because of an additive effect on blood pressure.

Hypertension and chest pain are potential adverse effects. More common adverse effects include asthenia, nausea, dizziness and somnolence. The frequency of adverse effects increases with the dose.

The safety of eletriptan in pregnancy is uncertain. Small amounts are excreted in breast milk.

In clinical trials, 54–65% of patients responded within two hours to a dose of 40 mg eletriptan. The headache returned within 24 hours in 23% of patients. A second dose can be taken, if more than two hours have passed since the first dose. There is no point in taking a second dose if there was no response to the first dose.

More patients will respond within two hours to eletriptan than to sumatriptan. In one study 67% of 779 patients taking eletriptan 40 mg improved compared with 59% of 799 patients taking sumatriptan 100 mg. Both drugs were more effective than placebo, because only 26% of the 404 patients in the placebo group responded.[1]

A company-supported meta-analysis has compared eletriptan and sumatriptan. There were 19 randomised placebo-controlled trials of the drugs involving several thousand patients. Compared to sumatriptan 100 mg, a mean of 9.1% more patients will obtain pain relief two hours after taking eletriptan 40 mg.[2]

Another analysis funded by the company compared eletriptan with other members of the class. The numbers of patients who needed to be treated for one to have a 24-hour sustained response were 3.6 for eletriptan 40 mg, 4.9 for sumatriptan 100 mg, 4.5 for zolmitriptan 5 mg and 5.7 for naratriptan 2.5 mg.[3]

T T T manufacturer provided clinical evaluation

References

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Icatibant

Firazyr (Shire Australia)

pre-filled syringe containing 30 mg/3 mL solution

Approved indication: hereditary angioedema

Australian Medicines Handbook Appendix A

Hereditary angioedema is a rare condition which is characterised by attacks of swelling that can occur anywhere in the body including face, larynx, gut or limbs. It can be painful, particularly with gastrointestinal attacks, and if the larynx is affected asphyxiation and death can occur. Most untreated patients will experience at least one acute attack a month which typically lasts for a few days.

The condition is caused by the absence or dysfunction of the C1 esterase inhibitor. This is thought to lead to increased vascular permeability due to unregulated bradykinin activation.

Icatibant, a synthetic decapeptide, has a similar structure to bradykinin and acts as a competitive antagonist blocking the receptors that bradykinin normally attaches to. Inhibiting bradykinin during an acute attack reduces ongoing inflammatory processes. Treatments for histamine-induced angioedema, such as corticosteroids, antihistamines or adrenaline, have no effect in patients with hereditary angioedema.

In a pilot study of 15 patients with hereditary angioedema, icatibant, given intravenously or subcutaneously, reduced

recovery time from acute attacks compared to historical data from untreated attacks.[1] Based on these findings, randomised controlled trials were conducted.

In a head-to-head trial, subcutaneous icatibant (30 mg) was compared to oral tranexamic acid, another treatment for hereditary angioedema (FAST-2 trial). The median time to onset of symptom relief was shorter for icatibant than tranexamic acid (2 hours vs 12 hours) in the 74 patients.[2]

Icatibant also brought more rapid symptom relief from attacks compared to placebo (2.5 hours vs 4.6 hours) in another study trial of 56 patients (FAST-1 trial). However, this difference was not statistically significant. Not all patients in the controlled trials responded to icatibant immediately – four hours after the start of treatment, 20–33% of patients had not responded.[2]

Icatibant is given as a 3 mL subcutaneous injection in the abdomen so it is not surprising that the most common adverse events are injection-site reactions. These include erythema, swelling, burning, itching and pain. Recurrent angioedema attacks have been reported as serious adverse events with icatibant, but the relationship of these to treatment is unclear.

After injection, icatibant is rapidly absorbed with maximum concentrations being reached after about 30 minutes. It has a terminal half-life of 1–2 hours and its metabolites are mainly excreted in the urine. Cytochrome P450 enzymes are not involved in the metabolism of icatibant and dose adjustments are not needed in renal and hepatic impairment.

Bradykinin has been implicated in the protection of the myocardium during ischaemia. Icatibant could potentially antagonise this protective effect so it should be used with caution in people with acute ischaemic heart disease, unstable angina pectoris or those who have recently had a stroke. Icatibant is not indicated for children.

It is not known if neutralising antibodies develop to icatibant. So far, no signs of increasing hypersensitivity have been observed in patients who have received repeated doses. With adequate training, patients can self-administer icatibant if the doctor thinks it is appropriate. However, if the symptoms are not resolving after two hours, or if the face, lips or pharyngeal area are affected, patients should seek immediate medical help.

Icatibant appears to be an effective treatment for hereditary angioedema, more so than tranexamic acid. It is not known how icatibant will compare to human C1 esterase inhibitor, another recently approved treatment for hereditary angioedema (Aust Prescr 2010;33:89-95).

T T T manufacturer provided clinical evaluation

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Omega-3-acid ethyl esters

Omacor (Abbott)

1000 mg capsules

Approved indications: hypertriglyceridaemia, secondary prevention following myocardial infarction

Australian Medicines Handbook section 6.5.4

A diet rich in fish oils has long been associated with cardiovascular benefits.[1] The components of fish oil include omega-3 polyunsaturated fatty acids. Ethyl esters of two of the acids, docosahexaenoic acid and eicosapentaenoic acid, are contained in the new product. There is currently no complete explanation of how these esters act on triglycerides and the cardiovascular system.

There have been several studies of omega-3-acids and a meta-analysis found that they significantly reduce triglyceride concentrations by 0.3 mmol/L.[2] In an early study, 57 patients with combined hyperlipidaemia were randomised to take the esters or corn oil as an adjunct to diet. After 12 weeks serum triglycerides had reduced by 28% (estimated 1.12 mmol/L absolute change) in the 28 patients who took the esters, but only slightly reduced in those given corn oil. Both treatments significantly reduced total cholesterol, but only slightly increased high density lipoprotein (HDL) cholesterol.[3]

The product has also been studied in 59 patients with serum triglycerides above 2.3 mmol/L who were taking simvastatin. They were randomised to add the omega-3-acid ethyl esters or a placebo for 24 weeks. Serum triglycerides fell from a mean of 4.6 to 3.5 mmol/L with active treatment, but the mean increased with placebo from 3.8 to 3.9 mmol/L. These changes were unrelated to the patients' simvastatin doses.[4]

A larger trial also studied hypertriglyceridaemia in patients taking simvastatin. After dietary advice and taking open-label simvastatin for eight weeks, 256 patients were randomised to add omega-3-ethyl esters or placebo. After a further eight weeks the mean triglyceride concentration had fallen from a baseline value of 282 mg/dL to 202.4 mg/dL (3.19 to 2.29 mmol/L) with the esters and from 286.7 to 275.9 mg/dL (3.24 to 3.12 mmol/L) with placebo. HDL cholesterol increased by 1.8 mg/dL (0.047 mmol/L) with the esters and decreased by 0.7 mg/dL (0.018 mmol/L) with placebo.[5]

The indications for using the esters in hypertriglyceridaemia are restricted. The product is only approved as monotherapy for type IV and V dyslipidaemia. It can be added to therapy of type IIb dislipidaemia if a 'statin' does not produce adequate control.

The main study supporting the use of the esters in secondary prevention after myocardial infarction involved 11 324 patients. They were randomised to take vitamin E, the esters, both or neither. After 3.5 years the relative risk of death, non-fatal myocardial infarction and non-fatal stroke had reduced by 10% in the patients who took the esters compared with those who did not. There was a 26% reduction in the risk of sudden death. Adding vitamin E to the esters did not significantly add to their efficacy.[6] The dose used was 25% of the 4 g recommended for dyslipidaemia so there were only small changes in lipids. This suggests that another mechanism may explain the beneficial effects of the esters after myocardial infarction.

Approximately 4% of patients will stop taking omega-3-acid esters because of adverse effects. Compared with placebo, patients taking them complain more frequently of altered taste and gastrointestinal upsets. Liver function should be monitored in patients with liver dysfunction. Fish oils may prolong the bleeding time, within normal limits, so this effect should be considered if the patient is being anticoagulated or taking aspirin. High doses may increase the concentration of low-density lipoprotein cholesterol. It is uncertain if patients who are allergic to fish have an increased risk of adverse reactions.

Fish oils are an option in the treatment of certain dyslipidaemias. The amount required cannot easily be obtained from the diet. Eating oily fish several times a week may be enough for patients after myocardial infarction. Although the secondary prevention trial showed benefits, they depended on how the data were analysed. In one analysis the esters did not have a significant effect on cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes. A systematic review of omega-3-fatty acids found they did not significantly reduce the risk of death or cardiovascular events.[7] If they are used for secondary prevention, it is important that the patient also takes the standard therapies used after myocardial infarction.

T T manufacturer provided additional useful information

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Pazopanib

Votrient (GlaxoSmithKline)

200 mg and 400 mg tablets

Approved indication: metastatic renal cell carcinoma

Australian Medicines Handbook section 14.2.2

Renal cell tumours tend to be very vascular and are insensitive to chemotherapy (Aust Prescr 2006;29:151–3). Pazopanib, previously GW786034, works by inhibiting the formation of new blood vessels and preventing tumour growth. It inhibits tyrosine kinase by binding to several targets including vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, platelet derived factor receptor-α and -β, and the cytokine receptor c-kit.

There are a number of other angiogenesis inhibitors with a similar action to pazopanib. These include sorafenib, sunitinib and bevacizumab (Aust Prescr 2006;29:9–12 and 2006;29:13–5).

The approval of pazopanib is based on a phase III placebo-controlled trial of 435 patients with locally advanced or metastatic renal cell carcinoma. (About half of these people had previously received cytokine-based treatment such as interferon-alfa or interleukin-2.) Patients took pazopanib until their disease progressed or they died, or they could not tolerate treatment. The median duration of treatment was 7.4 months with pazopanib and 3.8 months with placebo. Oral pazopanib 800 mg (once daily) significantly prolonged progression-free survival compared to placebo (median duration of 9.2 months vs 4.2 months). In terms of tumour response, one patient out of 290 had a complete response to pazopanib and almost a third (87) had a partial response. In the placebo group, there were no complete responses and only 3% of patients (5/145) had a partial response.[1] Overall survival was not statistically different between groups at the time of the analysis.

In the pazopanib group, diarrhoea (52%), hypertension (40%), change in hair colour (38%), nausea (26%), anorexia (22%) and vomiting (21%) were the most common adverse events. More patients dropped out because of adverse events in the

pazopanib group than in the placebo group (14% vs 3%). Arterial thrombotic events (myocardial infarction or ischaemia, cerebrovascular accident) occurred in 3% of patients and 13% had a haemorrhagic event. Just over half of the patients had elevated liver enzymes (serum transaminases, bilirubin) and some of these people had to discontinue treatment. Serious adverse events (grade 3 or 4) to pazopanib were experienced by 40% of patients.[1] Nine of these patients died – reasons included bleeding (4 patients), cardiac event (3), hepatic failure (1) and gastrointestinal perforation (1).

After oral administration, peak concentrations of pazopanib are reached after 2–4 hours. Food increases exposure to this drug so it should be taken on an empty stomach (at least one hour before or two hours after a meal). Tablets should not be crushed as this may affect their rate of absorption. Pazopanib is mainly metabolised by cytochrome P450 3A4, and to a lesser extent by CYP1A2 and CYP2C8. It has a mean half-life of 31 hours and is mainly eliminated in the faeces.

Dose reduction of pazopanib should be considered if strong inhibitors of CYP3A4, such as ketoconazole, ritonavir or clarithromycin, are given concomitantly. Grapefruit juice should be avoided. Inducers of CYP3A4 (rifampicin) may decrease plasma concentrations of pazopanib, and if they cannot be avoided, pazopanib should not be given. Pazopanib use is not recommended with drugs that have a narrow therapeutic window and are metabolised by CYP3A4, CYP1A2 and CYP2C8.

Because of the risk of hepatotoxicity, liver function should be assessed before starting pazopanib and regularly during treatment. Pazopanib may need to be reduced, interrupted or discontinued depending on the results of liver function tests, and specific recommendations are given in the product information. People with moderate hepatic impairment should be given a reduced daily dose and pazopanib is not recommended in patients with severe hepatic impairment.

QT prolongation and torsades de pointes have been reported so pazopanib should be used with caution in patients who have a history of QT prolongation or relevant cardiac disease, or who are taking drugs that prolong the QT interval (see Aust Prescr 2002;25:63–5). In addition, doctors should be cautious when giving pazopanib to patients who have a history or are at increased risk of myocardial infarction, angina, ischaemic stroke and transient ischaemic attack.

As fatal haemorrhage has occurred, pazopanib should not be given to patients with a history of haemoptysis, or cerebral or significant gastrointestinal haemorrhage in the previous six months. Patients with cerebral metastases were excluded from the trials. Fatal gastrointestinal perforation has also been reported and doctors should be vigilant for symptoms.

Hypertension is a common adverse effect of pazopanib and mostly occurs in the first 18 weeks of treatment. Patients should be monitored before starting pazopanib and during treatment. If antihypertensive therapy is not effective, the dose of pazopanib may need to be reduced or discontinued.

Hypothyroidism developed in some patients taking pazopanib so monitoring of thyroid function is recommended. Proteinuria has also occurred – including one serious case – so periodic urinanalysis is advised.

Although pazopanib prolongs median progression-free survival by five months, the risks of adverse effects are considerable. Fatal adverse events – including hepatic toxicity – have occurred with an approximate death rate of 2.2%. Patients should be informed of these risks before deciding whether to start treatment.

It is not known how the efficacy of pazopanib compares to other treatments for renal cell carcinoma but a phase III comparative trial with sunitinib is ongoing.

[T] manufacturer provided only the product information

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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.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/pmeds/auspar.htm)

Answers to self-test questions

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