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Conflict of interest: none declared

There is a Comment for consumers online with this article at www.australianprescriber.com/magazine/33/1/19/22

Self-test questions

The following statements are either true or false (answers on page 27)

3. Reactions to contrast media may occur up to a week after the procedure.
4. Patients with renal impairment should not take metformin when receiving contrast media.

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.

Ambrisentan

Volibris (GlaxoSmithKline)

5 mg and 10 mg film-coated tablets

Approved indication: pulmonary arterial hypertension

Australian Medicines Handbook section 6.7

Pulmonary arterial hypertension may be idiopathic or be associated with other conditions such as connective tissue disease. The severity of pulmonary arterial hypertension is classified (I–IV) according to its effect on the patient's physical activity. Conventional treatment includes diuretics and warfarin, but more severe cases may need treatment with prostacyclins, such as epoprostenol, or endothelin receptor antagonists, such as bosentan and sitaxentan.

Ambrisentan is a selective antagonist of the endothelin type A receptor. This action blocks the vasoconstrictive effect of endothelin, a peptide produced by endothelial cells.

Like bosentan and sitaxentan, ambrisentan is taken orally. The tablets should not be chewed or crushed, but food does not affect bioavailability. Most of the dose is metabolised and excreted from the gut. The effective half-life is approximately nine hours. As the enzymes involved in the metabolism include cytochrome P450 3A4 and 2C19 there is a potential for drug interactions, but their clinical significance is currently unclear. Ambrisentan is not recommended for patients with liver disease, or if the patient has transaminase concentrations more than three times the upper limit of normal.

A dose-ranging study enrolled 64 patients with symptomatic pulmonary arterial hypertension despite conventional therapy. They could only walk an average of 343 metres in six minutes at the start of the study. After 12 weeks this had increased by approximately 36 metres irrespective of the dose. Pulmonary artery pressure decreased and there was less dyspnoea.¹

Ambrisentan was then compared with placebo in two trials which randomised 394 patients. At the start of the study these patients could only walk an average of 340–355 metres in six minutes. One study used 5 mg or 10 mg doses. After 12 weeks these doses had increased the distance the patients could walk by 31–51 metres more than placebo. The other trial tested 2.5 mg and 5 mg. These doses increased the distance covered in six minutes by 32–59 metres more than placebo. A group of 280 patients completed an extension of the studies. After 48 weeks of taking ambrisentan they were able to walk 39 metres further than they were able to at the start of the studies.²

Ambrisentan's adverse effects and interactions will become clearer with more widespread use. The most frequent adverse effects in the trials, occurring more often than with placebo, were peripheral oedema, nasal congestion, sinusitis, flushing and palpitations.² Fluid retention may present as decompensated heart failure. Hepatic function must be monitored at least once a month because of the risk of liver damage. Haemoglobin should also be measured regularly as anaemia can occur in 7% of patients. Ambrisentan is contraindicated in pregnancy.

Although ambrisentan is the seventh drug to be approved for pulmonary arterial hypertension in recent years, the clinical benefit of these drugs is unclear. While they improve the six-minute walk test, this is a surrogate outcome. Their effect on survival is uncertain. There is also a need to compare the effectiveness of these drugs in longer-term studies.

✘ manufacturer did not respond to request for data

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Golimumab

Simponi (Schering-Plough)

prefilled syringe or autoinjector containing 50 mg in 0.5 mL

Approved indications: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis

Australian Medicines Handbook section 15.2.1

Treatment with tumour necrosis factor inhibitors improves the signs and symptoms of severe autoimmune inflammatory joint diseases. Golimumab is a recombinant human monoclonal antibody that binds to tumour necrosis factor alpha, blocking its activity. It has been approved for several indications in Australia including:

- rheumatoid arthritis, in combination with methotrexate when other treatments have failed
- psoriatic arthritis, alone or in combination with methotrexate when other treatments have failed
- ankylosing spondylitis in adults.

Following subcutaneous injection, maximum serum concentrations of golimumab are reached within two to six days. Steady-state serum concentrations are reached after 12 weeks following monthly injections of golimumab 50 mg. The mean terminal half-life ranges from 11 to 14 days. The clearance of golimumab is increased in patients with anti-golimumab antibodies, but it is unclear what effect these antibodies have on safety and efficacy. Treatment with concurrent methotrexate reduces the number of patients who develop antibodies.

The efficacy of golimumab for moderate to severe active rheumatoid arthritis has been shown in three placebo-controlled trials totalling 1542 patients.¹⁻³ Patients in the trials had at least four swollen or tender joints. Golimumab

50 mg or 100 mg, or placebo, was given subcutaneously with or without methotrexate every four weeks. Response to treatment was measured according to the American College of Rheumatology 20% improvement (ACR20) or 50% improvement (ACR50) criteria. These are composite outcomes that assess the number of swollen and tender joints, the erythrocyte sedimentation rate or C-reactive protein concentration and global assessments of arthritis activity by the patient and doctor.

In the GO-FORWARD trial (444 patients), over half of the patients receiving golimumab plus methotrexate (55.1% with 50 mg and 56.2% with 100 mg) had a 20% improvement in symptoms by week 14, versus only a third receiving placebo plus methotrexate. Patients receiving golimumab with methotrexate also reported improvements in their physical function after 24 weeks. There were 12 serious infections during the trial – 11/311 patients receiving golimumab and 1/133 patients receiving placebo. One of the patients who had received two doses of golimumab 100 mg died from sepsis after developing pneumonia. None of the 92 patients who were being treated for latent tuberculosis (usually isoniazid) at baseline developed active infection during the trial. Three patients receiving the study drug had malignancies – these were squamous cell cancer, basal cell cancer and breast cancer.¹

The GO-AFTER trial enrolled 461 patients who had previously used tumour necrosis factor inhibitors. They were allowed to continue methotrexate, sulfasalazine or hydroxychloroquine. After 14 weeks, significantly more patients had responded to golimumab than to placebo (ACR20: 35% with 50 mg and 38% with 100 mg vs 18% with placebo). Two patients receiving the study drug developed cancer – one was squamous cell carcinoma and the other was lymphoma. There were six serious infections with golimumab (pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection, urosepsis).²

In the GO-BEFORE trial, which enrolled 637 patients who had not previously received methotrexate, the primary end point was not met. However, in a post hoc modified intention-to-treat analysis, more patients receiving golimumab plus methotrexate had a 50% improvement in their symptoms by week 24, compared to those receiving placebo plus methotrexate (ACR50: 40.5% with 50 mg and 36.5% with 100 mg vs 29.4% with placebo). Unexpectedly, only the response rate to the lower golimumab dose was significantly better than placebo. The response of patients who received golimumab alone without methotrexate was not that different to those given placebo plus methotrexate (ACR50: 33.1% vs 29.4%).³

Nausea was the most common adverse event with golimumab plus methotrexate (13.9–15.1% vs 10% with

placebo and methotrexate). Other frequent events included elevated aspartate aminotransferase, elevated alanine aminotransferase, upper respiratory tract infection, dyspepsia and headache. There were two deaths in the trial – both patients were receiving golimumab. One death was from suicide, the other from cardiorespiratory arrest after surgery for a gluteal abscess. Two of the four malignancies that occurred in the trial were in patients receiving golimumab (breast cancer, Hodgkin's lymphoma). A patient receiving the higher golimumab dose was diagnosed with spinal tuberculosis (requiring surgery) eight weeks into the trial.³

Golimumab has also been assessed in patients with active psoriatic arthritis (three or more swollen or tender joints) in the GO-REVEAL trial. This study enrolled patients who had not previously received tumour necrosis factor inhibitors. Patients were allowed to continue methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids but were randomised to add injections of placebo (113 patients), golimumab 50 mg (146 patients) or golimumab 100 mg (146 patients) every four weeks. After 14 weeks, significantly more patients responded to golimumab than placebo (ACR20: 51% with 50 mg and 45% with 100 mg vs 9% with placebo). Patients receiving golimumab also had improvements in physical functioning and psoriasis symptoms (skin and nails). These benefits were irrespective of methotrexate use.

In the GO-REVEAL trial, upper respiratory tract infections and nasopharyngitis were the most commonly reported adverse events with golimumab and occurred more frequently than with placebo (10% and 10% with golimumab vs 6% and 4% with placebo). Elevated aspartate aminotransferase and alanine aminotransferase also occurred more frequently than with placebo. Alanine aminotransferase was increased in 24% of patients with golimumab 50 mg, 35% with golimumab 100 mg and 18% with placebo. Three malignancies were reported in the trial. These were in patients receiving the higher golimumab dose and included two cases of basal cell carcinoma and one case of prostate cancer. Other cancers were reported after the study period in patients who had received golimumab. These included small cell lung cancer (two cases), colon cancer, and basal cell carcinoma (two cases). A case of liver histoplasmosis was also reported in a patient who received golimumab.⁴

Golimumab has also shown benefit in people with ankylosing spondylitis (GO-RAISE trial). (Concurrent treatment with methotrexate, sulfasalazine, hydroxychloroquine, corticosteroids and NSAIDs was allowed during the trial.) Of the 356 adults enrolled in the study, significantly more people randomised to monthly

golimumab had a 20% improvement in their symptoms compared to those in the placebo group (59.4% with 50 mg and 60% with 100 mg vs 21.8%) after 14 weeks. Patients in the golimumab group also reported significant improvements in back pain, morning stiffness and pain at night, but not in range of motion. There were more infections with golimumab than placebo. Similarly, fatigue, headache, diarrhoea, injection-site erythema and elevated aspartate aminotransferase and alanine aminotransferase concentrations were more common with the study drug than with placebo. One patient on the lower dose of golimumab had a myocardial infarction despite normal cardiac assessment at baseline.⁵

As golimumab affects the immune system there is a risk of serious infection, particularly in the elderly. Patients with active tuberculosis or other severe or opportunistic infections should not be given golimumab. If a patient tests positive for latent tuberculosis, they should be referred to a specialist for appropriate treatment before starting golimumab. It is important to monitor patients for infections while they are receiving golimumab. As the drug takes up to five months to clear from the body, patients should also be monitored after treatment has stopped. Patients should not be given live vaccines.

Golimumab has been associated with elevated liver enzymes so hepatic function should also be monitored during treatment.

Cancers, such as lymphoma, have occurred in patients given golimumab so caution is urged when prescribing this drug for patients who have a history of malignancy or develop a malignancy. Care should also be taken in patients with demyelinating disorders as golimumab can exacerbate these conditions.

Golimumab is contraindicated in moderate to severe heart failure. It should not be given with anakinra or abatacept. Some patients in the trials developed antinuclear antibodies following golimumab treatment, although none of them developed lupus-like symptoms.

A 50 mg dose of golimumab is recommended. It should be given subcutaneously once a month and patients may be able to do this themselves after training.

Golimumab was effective in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, and there seemed to be no advantage of the 100 mg dose over the 50 mg dose. Due to the lack of comparative trials, it is not known how it will compare to other tumour necrosis factor inhibitors currently used, although the fact that it can be self-administered once a month may be preferred by some patients.

✘ manufacturer declined to supply data

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Lacosamide

Vimpat (UCB Pharma)

50 mg, 100 mg, 150 mg and 200 mg tablets

Approved indication: partial seizures

Australian Medicines Handbook section 16.1.3

Many patients with epilepsy have partial seizures and these can become generalised. Carbamazepine or valproate are often used, but some patients require more than one drug to keep them free of seizures. Drugs which can be added on include gabapentin, lamotrigine, levetiracetam and now lacosamide.

The exact mechanism of action of lacosamide is uncertain. It is thought to stabilise neuronal membranes by enhancing the slow inactivation of voltage-gated sodium channels.

Oral doses of lacosamide are completely absorbed. Twice-daily doses produce steady-state concentrations after three days. Metabolism of the drug includes cytochrome P450 2C19, but 40% of the dose is excreted unchanged. As most of the drug and its metabolites are excreted in the urine, doses may need to be limited in patients with severe renal or liver impairment. The elimination half-life of lacosamide is approximately 13 hours.

The safety and efficacy of lacosamide was assessed in a trial which randomised 421 adults with simple or complex partial-onset seizures, with or without generalisation. These patients were having seizures despite having taken at least two anticonvulsants. They were randomised to add a placebo or lacosamide 200 mg, 400 mg or 600 mg daily. After dose titration, the patients were maintained on these doses for 12 weeks. The median reduction in seizure frequency was 39% with 400 mg and 40% with 600 mg. While lacosamide 200 mg reduced seizure frequency by 26% this was not significantly different from the 10% reduction in the placebo group.¹

The 200 mg and 400 mg doses were studied in a similar placebo-controlled trial involving 485 adults. During 12 weeks of maintenance treatment, the median reduction in seizure frequency per 28 days was 35% with 200 mg and 36% with 400 mg daily. These reductions were significantly greater than the 21% reduction in the group who added placebo.² Another study of 421 patients also found a 21% reduction in the placebo group, while lacosamide 400 mg and 600 mg reduced seizure frequency by 37% and 38%.

The intravenous formulation of lacosamide can be used when patients are unable to take their tablets, for example because of surgery. As the tablets have very high bioavailability the intravenous dose is the same as the oral dose.³

In the clinical trials the most frequent adverse reactions were dizziness, altered vision, headache, nausea and vomiting. As the adverse effects were more frequent with lacosamide 600 mg, the maximum total daily dose for patients with normal renal function is 400 mg. There is also a dose-dependent prolongation of the PR interval on the ECG. Second or third degree heart block is therefore a contraindication to lacosamide.

The efficacy and safety of lacosamide in children and pregnant or lactating women is unknown. There was an increase in stillbirths in studies of pregnant animals.

While lacosamide adds to the choice of adjunctive anticonvulsants for partial seizures, not many patients became seizure free in the trials. Approximately 34% of patients taking lacosamide 200 mg daily will have a greater than 50% reduction in seizure frequency, but this is not always statistically different from placebo.^{1,2} Some patients may have an increased number of seizures.¹ As the trials were relatively short for a chronic condition, there is a possibility that serious adverse reactions could emerge. One healthy volunteer developed hepatitis and nephritis after taking lacosamide. There may also be an increase in suicidal thoughts.

T manufacturer provided only the product information

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Prasugrel

Effient (Eli Lilly)

5 mg and 10 mg tablets

Approved indication: recurrent myocardial infarction

Australian Medicines Handbook section 7.2.2

Patients with myocardial infarction are at high risk of recurrence. Dual antiplatelet therapy, such as aspirin and clopidogrel, has been shown to reduce this risk.

Prasugrel, an adenosine diphosphate receptor antagonist of the thienopyridine class, is a new antiplatelet drug. It works by inhibiting platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ receptor on platelets. After oral administration, prasugrel is metabolised mainly by cytochrome P450 3A4 and 2B6. Its elimination half-life is 7.4 hours with the majority of the dose being excreted in the urine.

In a pharmacodynamic study of patients with acute coronary syndrome, prasugrel (60 mg loading dose, then 10 mg daily) was found to be a more potent inhibitor of platelet aggregation than clopidogrel (600 mg loading dose then 150 mg daily) in ex vivo blood tests.¹

The approval of prasugrel is based on a comparative trial with clopidogrel in 13 608 patients. These people had acute coronary syndrome (10 074 with unstable angina or non-ST-elevation myocardial infarction and 3534 with ST-elevation myocardial infarction) and nearly all of them were undergoing percutaneous coronary intervention. Both prasugrel (60 mg loading dose then 10 mg daily) and clopidogrel (300 mg loading dose then 75 mg daily) were given in conjunction with aspirin (75–162 mg). The median duration of treatment was 14.5 months. The primary end point was a composite of cardiovascular death, non-fatal myocardial infarction or stroke. Significantly fewer patients receiving prasugrel had a cardiovascular event compared to those receiving clopidogrel (9.9% vs 12.1%). This was mostly due to the reduced incidence of myocardial infarction. Rates of stroke and death from cardiovascular causes

not involving myocardial infarction were similar between groups. There were also significant reductions in the rates of stent thrombosis and urgent target-vessel revascularisation procedures with prasugrel. In the 3146 people with diabetes, less patients in the prasugrel group had a cardiovascular event than in the clopidogrel group (12.2% vs 17%).²

Obviously with antiplatelet drugs there is a risk of bleeding. The incidence of major haemorrhage in the trial was greater with prasugrel than with clopidogrel (2.4% vs 1.8%). This was fatal for 21 (0.4%) patients taking prasugrel and 5 (0.1%) patients taking clopidogrel. A post hoc analysis of harm versus benefit (based on bleeding and cardiovascular events) found that certain groups of patients did not benefit from prasugrel treatment. This included patients aged 75 or older and those weighing less than 60 kg. Prasugrel is not generally recommended for patients over 75 years but if the doctor decides it would benefit the patient, a lower maintenance dose (5 mg) is advised. Similarly, a lower maintenance dose is recommended if prasugrel is given to patients weighing less than 60 kg. Doctors should be aware that there is no evidence for the safety or efficacy of the lower dose of prasugrel. The post hoc analysis found that patients who had had a previous stroke or transient ischaemic attack had net harm and should not be given prasugrel.

Other adverse events included severe thrombocytopenia (0.3%), neutropenia (less than 0.1%) and colonic neoplasms (0.2%). Colonic cancers were reported twice as often with prasugrel than with clopidogrel, possibly because they were more likely to be detected due to the increased bleeding risk.¹

Caution is urged when giving prasugrel to patients who have an increased risk of bleeding. This includes patients taking concomitant drugs, such as oral anticoagulants, non-steroidal anti-inflammatory drugs and fibrinolytics. Care should also be taken in patients who have had recent surgery, recurrent gastrointestinal bleeding or active peptic ulcers. To prevent bleeding complications, prasugrel should be stopped at least seven days before elective surgery. Premature discontinuation of prasugrel can increase the risk of thrombosis, myocardial infarction and death so in this situation patients should be monitored for cardiac events. It is contraindicated in patients with severe hepatic impairment.

Although prasugrel is metabolised by CYP3A4 it can be used concomitantly with other drugs metabolised by this pathway, such as the statins. It can also be given with digoxin, proton pump inhibitors and H₂ blockers. As prasugrel is a weak inhibitor of CYP2B6, a clinically significant effect may be seen when it is co-administered with drugs that are solely metabolised by CYP2B6 and have a narrow therapeutic window (such as cyclophosphamide or efavirenz).

When used with aspirin, prasugrel provides an alternative to other antiplatelet drugs for preventing atherothrombotic events in some patients with acute coronary syndrome who are undergoing percutaneous coronary intervention. However, there are only short-term clinical data for this drug (up to 15 months). Prasugrel appears to have more potent antiplatelet effects than clopidogrel so the risk of bleeding is higher.

T manufacturer provided additional useful information

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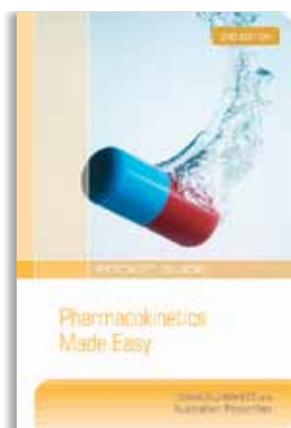
The T-score (**T**) is explained in 'New drugs: transparency', *Aust Prescr* 2009;32:80-1.

* 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.emea.eu).

Erratum

The Medicines Line phone number is 1300 888 763.



Pharmacokinetics made easy

The second edition of this pocket guide by Donald Birkett will be useful for a wide audience of health professionals and students. The individual chapters were first published as a series of articles in *Australian Prescriber* to assist practitioners with drug dosing. The physiological approach addresses clinical issues in drug therapy and makes them directly applicable to practice situations.

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Answers to self-test questions

1. False
2. False
3. True
4. True

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