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.

Dabigatran etexilate

Pradaxa (Boehringer Ingelheim)

75 mg and 110 mg capsules

Approved indication: prevention of postoperative venous thrombosis

Australian Medicines Handbook section 7.1

Patients who have had major surgery on their legs are at risk of venous thrombosis. This risk can be reduced by anticoagulation with a heparin or an alternative such as fondaparinux. A disadvantage of these drugs is that they have to be given by injection, so patients may not continue them after leaving hospital. An oral anticoagulant, without the disadvantages of warfarin, might improve the effectiveness of prophylaxis.

Dabigatran is a direct inhibitor of thrombin which can be taken orally as a prodrug (dabigatran etexilate). By inhibiting thrombin, it blocks the conversion of fibrinogen to fibrin and thus reduces clot formation. It is given 1–4 hours after surgery.

In healthy people dabigatran etexilate is rapidly absorbed and converted to dabigatran. Absorption is slower initially in postoperative patients, but subsequently peak plasma concentrations of dabigatran are reached two hours after a dose. The half-life, 12–14 hours, is also slightly longer after surgery. Treatment begins with half the ongoing dose. Most of the dose is excreted as dabigatran in the urine. People with reduced renal function, such as some elderly patients, may require a lower dose. If the creatinine clearance is under 30 mL/min, dabigatran is contraindicated.

A double-blind trial has compared dabigatran etexilate (220 mg and 150 mg daily) with a daily dose of subcutaneous enoxaparin 40 mg in 3494 people having total hip replacements. Treatment continued for 28–35 days until the patients had venography. However, many patients did not have venography so efficacy could only be assessed in 2651 patients. Death or venous thromboembolism occurred in 8.6% of the patients taking dabigatran 150 mg, 6% of those taking 220 mg and in 6.7% of the patients injected with enoxaparin.[1]

The same drugs and doses were used in a study of 2076 patients having total knee replacements. Treatment continued for 6–10 days. As some patients did not have venography, efficacy was assessed in 1541 patients. Death or venous thromboembolism occurred in 40.5% of the patients taking dabigatran 150 mg, 36.4% of those taking 220 mg and 37.7% of the enoxaparin group.[2]

Bleeding is a major concern when anticoagulants are used following surgery, and there is no antidote for dabigatran. After hip replacement, significant bleeding occurred in 1.3% of the dabigatran 150 mg group and 2.0% of the 220 mg group. This was fatal for one patient in each group. In the enoxaparin group 1.6% of patients had significant bleeding, but there were no fatalities.[1] After knee replacement the incidence of major bleeding was 1.5% in the dabigatran 220 mg group and 1.3% in the 150 mg and enoxaparin groups.[2] To reduce the risk of a haematoma forming, dabigatran should not be given for at least two hours following the removal of a spinal or epidural catheter.

Common adverse effects include nausea, vomiting, fever and constipation, but they occur irrespective of the treatment used. Routine monitoring is not required, but liver function should be checked before treatment as liver disease is a contraindication to dabigatran. Drugs which act on the P-glycoprotein transporter may alter the plasma concentration of dabigatran. These drugs include amiodarone, verapamil, clarithromycin and St John's wort. Quinidine is contraindicated. Anticoagulants and antiplatelet drugs such as clopidogrel are not recommended while the patient is taking dabigatran. Doses of aspirin above 75 mg daily increase the risk of bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used for short-term analgesia, but there may be an increased risk of bleeding particularly if the NSAID has a long half-life.

The main studies of dabigatran have shown that it has similar efficacy to enoxaparin, however an American study found inferior efficacy. In the USA prophylaxis can be given as enoxaparin 30 mg twice daily. The study of 1896 patients having knee replacement found venous thromboembolism in 31–34% of the patients taking dabigatran but in only 25% of those given enoxaparin.[3]

The development of the first direct thrombin inhibitor, ximelagatran, was halted because of concerns about adverse effects on the liver. Hepatotoxicity has not yet emerged as a significant problem with the relatively short-term use of dabigatran. If its safety and efficacy are confirmed in more widespread use, oral dabigatran may be a cost-effective alternative to subcutaneous low molecular weight heparins.

 manufacturer declined to supply data

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3. Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, et al; RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 2009;24:1-9.

Daptomycin

Cubicin (Novartis)

lyophilised powder for injection

Approved indications: skin infections, *Staphylococcus aureus* bacteraemia

Australian Medicines Handbook section 5.1

Daptomycin is a cyclic lipopeptide derived from a natural product of *Streptomyces roseosporus*. Its bactericidal effects stem from its ability to rapidly depolarise the membrane potential of Gram-positive bacteria. This causes inhibition of DNA, RNA and protein synthesis, and results in cell death.

It is indicated for adults with complicated skin and skin structure infections who require initial parenteral therapy and who are intolerant of alternative antibiotics (including those with penicillin allergy). It should only be used for infections suspected to be caused by susceptible Gram-positive bacteria.

Steady-state concentrations of daptomycin are reached after the third daily intravenous infusion. It is primarily excreted by the kidneys (mainly as unchanged drug) so dose adjustment is required for patients with severe renal insufficiency. Renal function and creatine kinase should be frequently monitored in these patients. In patients requiring haemodialysis, daptomycin should be administered after the procedure.

The efficacy of daptomycin (4 mg/kg intravenously once daily for 7–14 days) has been compared to a penicillin (cloxacillin, nafcillin, oxacillin or flucloxacillin) or vancomycin in two randomised trials with similar designs totalling 1092 participants. These patients were hospitalised mainly with complicated skin infections including wound infections, major abscesses, infected diabetic ulcers or other ulcers. Patients with mixed infections involving Gram-negative or anaerobic organisms were given concomitant aztreonam or metronidazole as appropriate. Among the clinically evaluable patients, treatment success rates for daptomycin were comparable to the comparator (83% vs 84%). However, in both groups success rates for methicillin-resistant *Staphylococcus aureus* infections were lower than for methicillin-sensitive *S. aureus* (75% vs 86% for daptomycin and 69% vs 87% for comparator). Success rates were also lower in patients aged 65 years or older.[1]

In another analysis of the trials looking only at patients with diabetic ulcers (mainly of the foot), 66% (31/47) of clinically evaluable patients benefited from daptomycin treatment compared with 70% (39/56) of patients treated with a penicillin or vancomycin. Methicillin-resistant *S. aureus* was isolated from ten patients; one received daptomycin and the rest received a comparator. After a course of treatment, infection was cleared in three of the comparator-treated patients but not in the daptomycin-treated patient.[2]

Adverse events were similar between groups with gastrointestinal disorders being the most common. Fifteen of the 534 patients (2.8%) receiving daptomycin developed elevated creatine kinase levels compared to ten of the 558 (1.8%) receiving the comparator.[1]

In Australia, daptomycin has also been approved for adults with bacteraemia caused by *S. aureus*, including those with right-sided native valve infective endocarditis caused by methicillin-susceptible or methicillin-resistant isolates. This approval was based on an open label randomised trial of patients with bacteraemia with or without left- or right-sided endocarditis. Daptomycin (6 mg/kg intravenously once daily) was compared to standard treatment consisting of gentamicin plus a penicillin (nafcillin, oxacillin or flucloxacillin) or vancomycin. (Patients in the daptomycin group who had left-sided endocarditis were also given gentamicin for the first four days.) The median duration of therapy was 14 days for daptomycin and 15 days for standard treatment.

Successful outcomes were reported in 53 of 120 (44%) patients receiving daptomycin and 48 of 115 (42%) patients receiving the comparator. In patients infected with methicillin-resistant isolates, success rates were similar for daptomycin but lower with standard treatment (44% vs 32%). Treatment failure was more often associated with persistent or relapsing *S. aureus* infection in the daptomycin group (15.8% of patients), whereas in the comparator group failure was more frequently associated with treatment-limiting adverse events. Therapy failed in all nine patients who had left-sided endocarditis caused by methicillin-resistant *S. aureus*, regardless of which treatment they received.[3]

Creatine kinase elevations were twice as common with daptomycin than with standard treatment (25% vs 12.5%). Adverse events related to the peripheral nervous system were also more common with daptomycin than with standard treatment (9.2% vs 1.7%), whereas renal impairment was more common with standard treatment than with daptomycin (18.1% vs 6.7%).[3]

Patients should be monitored for the development of muscle pain or weakness. Creatine kinase should be monitored weekly and more frequently in patients who have a higher risk of developing myopathy, such as those with severe renal insufficiency or taking other drugs that are associated with myopathy (HMG-CoA reductase inhibitors, fibrates, cyclosporin). Consider temporarily stopping HMG-CoA reductase inhibitors while patients are receiving daptomycin.

In patients taking concomitant warfarin, anticoagulant activity should be monitored during the first week of daptomycin therapy. Caution is urged when co-administering daptomycin with tobramycin.

Daptomycin-resistant bacteria have emerged in patients enrolled in the clinical trials. To reduce the development of daptomycin resistance, this antibiotic should only be used to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Daptomycin does not seem to be effective for infections caused by enterococci, including *Enterococcus faecalis* and *E. faecium*. Susceptibility of bacterial isolates should be monitored during the course of treatment.

Daptomycin provides another option for hospitalised adults with serious infections caused by Gram-positive pathogens. However, its efficacy may be lower in older adults. It can also be used for mixed infections involving Gram-negative or anaerobic bacteria if co-administered with appropriate antibiotics.

This antibiotic is not effective for left-sided endocarditis, or for pneumonia because it binds to surfactant and is inactivated. The efficacy of daptomycin in patients with prosthetic heart valves has not been demonstrated.

T manufacturer provided only the product information

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Etravirine

Intelence (Janssen-Cilag)

100 mg tablets

Approved indication: HIV

Australian Medicines Handbook section 5.4

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It binds to reverse transcriptase and blocks the RNA- and DNA-dependent activities of DNA polymerase. Etravirine is indicated for treatment-experienced adults with HIV who have evidence of viral replication and drug resistance to other antiretroviral drugs including NNRTIs.

The approval of etravirine is based on two identically designed randomised placebo-controlled trials (DUET-1 and DUET-2) in patients with advanced disease. These patients were resistant to currently available NNRTIs and had at least three primary mutations to protease inhibitors. All patients received darunavir (a protease inhibitor) boosted with ritonavir, as well as at least two other antiviral drugs. At the beginning of the studies the average viral load in enrolled patients was 70 000 copies/mL blood. The main measure of effectiveness for etravirine was the number of patients with less than 50 viral copies/mL. After 24 weeks of treatment, 59% (353/599) of patients who added etravirine (200 mg twice daily) had less than 50 viral copies/mL compared to 41% (248/604) of patients who added placebo. The mean increase in CD4 cells was 84 cells/microlitre in the etravirine groups and 65 cells/microlitre in the placebo groups. Using other active antiretroviral drugs with etravirine increases the likelihood of treatment response.[1,2]

The trials are ongoing and preliminary results presented at a conference reported that response rates to etravirine were maintained after 48 weeks of treatment (www.retroconference.org/2008/PDFs/790.pdf and www.retroconference.org/2008/PDFs/791.pdf). The total duration of the trials is expected to be 96 weeks.

Resistance to NNRTIs can develop easily. A single mutation in the reverse transcriptase gene of the virus can lead to reductions in susceptibility, often to all currently available inhibitors in the class. This broad cross-resistance limits the sequential use of other NNRTIs after treatment failure. In the DUET trials, decreased susceptibility to etravirine emerged and was associated with a number of different viral mutations. Cross-resistance with etravirine and other NNRTIs was also observed. The majority of viral strains containing two or three mutations conferring NNRTI resistance also had decreased susceptibility to etravirine.

The most common adverse events with etravirine are rash (17%), diarrhoea (15%) and nausea (14%). Rash was the most common adverse event for which patients discontinued treatment in the DUET trials (2% for etravirine, 0% for placebo). Severe and potentially life-threatening skin reactions, including

Stevens-Johnson syndrome, hypersensitivity reactions and erythema multiforme, have occurred in patients taking etravirine. Treatment should be stopped if this occurs. Other common adverse effects of etravirine include abdominal pain, tiredness and high blood pressure. Neuropsychiatric events occurred in 25% of patients taking etravirine. Similar numbers of events were seen in the placebo group.

Patients who also had hepatitis B and/or hepatitis C were included in the DUET trials, providing they were clinically stable. The incidence of hepatic events (such as hepatobiliary disorders) tended to be higher in patients taking etravirine compared to those taking placebo (11% vs 6%).

This drug should be taken after a meal to increase its bioavailability. Following oral administration, the maximum plasma concentration of etravirine is reached by four hours. Although etravirine is primarily metabolised by the liver, no dose adjustment is needed for patients with mild to moderate liver impairment. Etravirine has not been studied in patients with severe liver disease.

As etravirine induces CYP3A4 and inhibits CYP2C9 and CYP2C19, co-administration of drugs that are metabolised by these enzymes may affect the therapeutic or adverse effects of etravirine. Many drugs may interact with etravirine, including combinations of other antivirals. Etravirine should not be co-administered with other NNRTIs and there are specific recommendations about giving etravirine with protease inhibitors. Other drugs which potentially interact with etravirine include antiarrhythmics, anticoagulants, anticonvulsants, antifungals, antibiotics, benzodiazepines, corticosteroids, statins, immunosuppressants, phosphodiesterase type 5 inhibitors and St John's wort. It is therefore important to obtain a full record of the patient's medications before prescribing etravirine.

Etravirine represents another option for patients infected with multi-resistant HIV strains, although decreased susceptibility to this drug has been observed. Long-term data are needed to assess how durable the observed responses are. The patient's treatment history and antiviral resistance testing should guide the use of this drug.

☒ manufacturer declined to supply data

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Nitisinone

Orfadin (Orphan)

2 mg, 5 mg and 10 mg capsules

Approved indication: hereditary tyrosinaemia type 1

Tyrosine is one of the amino acids involved in the synthesis of molecules such as dopamine and noradrenaline. The metabolic pathway for tyrosine includes the enzyme fumarylacetoacetase. In hereditary tyrosinaemia there is a deficiency of this enzyme leading to accumulation of its substrates. This causes liver failure, renal tubular dysfunction and neurological crises. In the acute form of the disease death usually occurs before the child is one year old. Children with chronic forms of the disease are at risk of liver cancer. They need to have a diet with a restricted tyrosine intake.

Nitisinone blocks an earlier step in the metabolism of tyrosine. By competitively inhibiting the enzyme hydroxyphenylpyruvate dioxygenase it is thought to reduce the production of the toxic substrates of fumarylacetoacetase.

As hereditary tyrosinaemia type 1 is a rare disease, one of the early studies of nitisinone only included five children. During 7–9 months of treatment plasma and urinary markers of the toxic metabolites declined and liver function improved.[1]

The approval of nitisinone was based on an international, uncontrolled study of 207 children. They were treated for a median duration of 22 months. The biochemical markers improved and there was some evidence of improved survival. The four-year survival was 93%, but only 35 patients were included in that analysis. (Death or liver transplantation resulted in the withdrawal of 37 patients.) Compared to the treatment of historical controls with diet alone, the probability of surviving for four years increased from 29–60% to 88–94%. The occurrence of liver cancer was reduced, particularly in children who began treatment before their first birthday. Starting treatment before six months of age appears to reduce the need for liver transplantation.

As nitisinone blocks the metabolism of tyrosine, the plasma tyrosine concentration will increase. The patient therefore still needs to follow a diet deficient in tyrosine. High concentrations of tyrosine can have toxic effects on the eyes, skin and nervous system.

Nitisinone was originally developed as a herbicide, but development stopped when animal studies found it had ocular adverse effects. Ophthalmological assessment is needed before treatment and if ocular symptoms develop.

Patients need regular blood counts because leucopenia and thrombocytopenia can occur. These abnormalities may be transient but may require a reduced dose of nitisinone.

The pharmacokinetics of nitisinone have not been studied in detail. There are also no drug interaction studies.

Although it may be a lifelong treatment, much remains unknown about nitisinone. While it improves survival, it may not ameliorate the complications of the disease.[2] At present, the benefits of nitisinone with a low tyrosine diet do appear to outweigh the harms in treating hereditary tyrosinaemia type 1.

T T manufacturer provided additional useful information

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

T-scores are as follows:

T T T manufacturer provided clinical evaluation

T T manufacturer provided additional useful information

T manufacturer provided only the product information

T manufacturer declined to provide data

X manufacturer did not respond to request for data

* 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. True	3. True	5. False	7. False
2. False	4. False	6. True	8. False

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