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.

Cilostazol

Pletal (Pharmalink)

50 mg and 100 mg tablets

Approved indication: intermittent claudication

Australian Medicines Handbook section 6.8.1

Cilostazol is a phosphodiesterase III inhibitor. It is indicated for intermittent claudication in patients with peripheral arterial disease who do not have rest pain or evidence of peripheral tissue necrosis. Intermittent claudication is characterised by pain in the legs or buttocks during exercise which subsides with rest. These patients are usually managed by lifestyle modification, including stopping smoking and a supervised exercise program, plus drug therapy to reduce cardiovascular risk.

It is not clear exactly how cilostazol improves the symptoms of intermittent claudication. Its main physiological effects are vasodilation and inhibition of platelet aggregation. Other antiplatelet treatments with similar effects may reduce vascular events in peripheral artery disease, but they have not been shown to improve walking distance in patients with intermittent claudication.

A meta-analysis (seven trials involving 1500 patients) of cilostazol found that 50 mg and 100 mg cilostazol doses (given twice daily for 12–24 weeks) significantly increased absolute walking distance (maximum distance walked on a treadmill) from baseline by 32 m and 50 m more than placebo. A higher dose of cilostazol (150 mg twice daily) also increased walking distance, but the effect was not statistically significant.[1] Exclusion criteria varied between the trials but many excluded patients with ischaemic rest pain, hypertension, obesity and bleeding disorders. Patients taking antiplatelet, anticoagulant or anti-inflammatory drugs were also excluded from some of the trials.[1]

Only one of the studies in the meta-analysis compared cilostazol to an active comparator, pentoxifylline (400 mg three times daily). In this study, 698 patients with moderate to severe claudication received treatment for 24 weeks. Absolute walking distance increased by an average of 107 m for patients taking cilostazol, 64 m for pentoxifylline and 65 m for placebo.[2]

Cilostazol has not been directly compared to lifestyle interventions. However, a meta-analysis of supervised exercise programs found that after three months patients with intermittent claudication could walk 150 m further than those following an unsupervised exercise program. Before treatment, these patients could walk 300 m.[3]

The most common adverse events in the clinical trials were headache (more than 30% of patients), diarrhoea, palpitations and abnormal stools (more than 15%). Oedema resulted in some patients discontinuing cilostazol treatment.[4]

Phosphodiesterase inhibitors have previously been associated with increased mortality in patients with heart failure.[5] When cilostazol was approved in the USA, the Food and Drug Administration requested an additional long-term safety trial to assess all-cause mortality. Consequently, a postmarketing study followed 1435 patients with peripheral artery disease on cilostazol for up to 3.5 years. Patients taking aspirin, clopidogrel, pentoxifylline, anticoagulants, or who had had heart failure in the past, were allowed in the trial. It is important to note that patients with clinical evidence of current heart failure were excluded from this trial. From the data obtained, the number of deaths (from any cause or cardiovascular) and serious bleeding events were similar for cilostazol and placebo. There seemed to be no increase in bleeding events in patients taking aspirin, clopidogrel or anticoagulants.[4] However, long-term adherence in this study was low, with more than 60% of patients discontinuing before the end of the trial. This resulted in the study being underpowered to meet its primary end point – all-cause mortality – and limits the interpretation of the safety data.

After oral administration, cilostazol is readily absorbed and steady-state concentrations are reached after four days. A high fat meal increases the absorption of this drug and the recommendation is to take it at least half an hour before or two hours after breakfast and the evening meal. Smoking decreases exposure to cilostazol by approximately 20%.

Cilostazol is extensively metabolised mainly by CYP3A4 but also by CYP2C19 and CYP2D6, and is contraindicated in patients with moderate or severe hepatic impairment. The majority of metabolites are excreted in the urine so cilostazol is also contraindicated in severe renal impairment. Cilostazol may lead to increased plasma concentrations of drugs that are substrates of CYP3A4 or CYP2C19, such as midazolam, nifedipine and verapamil, so caution is recommended during co-administration.

Patients who are predisposed to bleeding, including those with active peptic ulceration, recent haemorrhagic stroke, surgery within the last three months, or proliferative diabetic retinopathy, should not take cilostazol. Cilostazol is also contraindicated in patients with congestive heart failure, prolonged QT_c interval, multifocal ventricular ectopic beats or

a history of ventricular tachycardia or ventricular fibrillation.

Haematological abnormalities (including thrombocytopenia, leucopenia, agranulocytosis, pancytopenia and aplastic anaemia) have occurred with cilostazol. Some of these were fatal so patients should have their blood counts monitored closely. Patients should be advised to report any signs of blood dyscrasia such as fever or sore throat, and if infection is suspected a full blood count should be done. Treatment should be stopped immediately if any haematological abnormalities develop. For patients having elective surgery, cilostazol should be stopped five days before the procedure.

Caution is urged when giving cilostazol with drugs that lower blood pressure as cilostazol may have an additive hypotensive effect with reflex tachycardia. Caution is also recommended when giving cilostazol to patients with atrial or ventricular ectopy or with atrial fibrillation or flutter.

Patients already taking anticoagulant or antiplatelet drugs should be monitored for bleeding events. Cilostazol has not been assessed in patients who are taking clopidogrel and have a high risk for bleeding such as coronary stent insertion. Cilostazol could potentiate the effects of nitric oxide donors such as sildenafil and should be used with caution in patients taking these drugs.

Cilostazol helps with the symptoms of intermittent claudication, however the overall gains were modest and show little advantage over supervised exercise programs.[3] Cilostazol should not be used in patients with congestive heart failure.

T T T manufacturer provided clinical evaluation

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Doripenem

Doribax (Janssen-Cilag)

500 mg powder for reconstitution and infusion

Approved indication: specified infections

Australian Medicines Handbook section 5.1.2

Doripenem is a new carbapenem with broad spectrum activity against Gram-negative or Gram-positive bacteria. However, it does not work against infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). This antibiotic is indicated for complicated intra-abdominal infections, nosocomial pneumonia (including ventilator-associated pneumonia) and complicated urinary tract infections (including pyelonephritis and cases of concurrent bacteraemia).

Doripenem is structurally related to the other carbapenems (ertapenem, imipenem, meropenem) which all have a beta lactam ring. The bactericidal activity of these antibiotics comes from their ability to inhibit cell wall synthesis by targeting the bacterial penicillin-binding proteins. In *in vitro* studies, doripenem has greater activity against *Pseudomonas aeruginosa*.

Doripenem is given by intravenous infusion every eight hours. For complicated intra-abdominal and urinary tract infections the infusion should be given over one hour, and over one or four hours for pneumonia. Doripenem is not extensively metabolised and most of the dose is excreted unchanged in the urine. Its half-life is approximately one hour in healthy adults.

A lower dose of doripenem is recommended for patients with moderate and severe renal impairment. Doctors should be particularly cautious when using this drug in patients with severely impaired renal function. Although doripenem is haemodialysable, there is insufficient evidence to recommend dose adjustment in those on dialysis. It is probably best avoided in these patients.

The efficacy of doripenem for complicated intra-abdominal infection was similar to that of meropenem in a randomised trial of hospitalised patients. Clinical cure rates (complete resolution or significant improvement of symptoms) were 86% for doripenem and 85% for meropenem in 319 microbiologically evaluable patients (21 to 60 days after completing treatment). More people with *P. aeruginosa* infections responded to doripenem than meropenem (favourable outcomes in 18/19 patients vs 15/19 patients), however this difference was not significant.[1]

Two open-label trials assessed the efficacy of doripenem for nosocomial pneumonia. The first trial compared doripenem to a combination of piperacillin and tazobactam in 444 patients, including some who were ventilated. The median duration of treatment was 11 days. Most patients also received amikacin because of the risk of *P. aeruginosa* infection. Clinical cure rates

were similar for doripenem and piperacillin/tazobactam (81% vs 80%) in the 253 clinically evaluable patients. Not surprisingly, cure rates were lower for patients who were ventilated (69% for doripenem vs 58% for piperacillin/tazobactam). In the doripenem group, four patients had emergent infections associated with drug-resistant bacteria, including *P. aeruginosa*, *Acinetobacter baumannii* and MRSA.[2]

In the other open-label pneumonia trial, doripenem (given as a 4-hour infusion) was found to be comparable to imipenem in 525 patients who required ventilation. Clinical cure rates were 68% for doripenem and 65% for imipenem in the clinically evaluable population (248 patients). More patients (microbiologically evaluable) with *Escherichia coli, Klebsiella pneumoniae* and *P. aeruginosa* infections responded to doripenem than imipenem. Drug resistance emerged in *P. aeruginosa* isolates during the trial, however this was more common with imipenem than with doripenem.[3] (Overall, 38% of patients in the trial were given adjunctive antibiotic treatment for either *P. aeruginosa* or MRSA.)

The efficacy of doripenem for complicated urinary tract infections and pyelonephritis was found to be comparable to levofloxacin in two trials totalling 1171 patients. One of the trials directly compared doripenem to levofloxacin, and the other trial was an open-label design which used the levofloxacin arm from the other trial for comparative analyses. (As yet, the results of these trials have not been published in full.)

In the pooled microbiologically evaluable populations, cure rates after 10 days of treatment were 82–84% for doripenem and 83% for levofloxacin. Microbiological cure rates were lower for renally impaired patients who received a lower dose of the intravenous study drug (75% (54/72 patients) for doripenem and 58% (15/26 patients) for levofloxacin). More infections emerged during doripenem treatment than levofloxacin treatment. Isolates included *Enterococcus faecali, E. coli, Enterobacter cloacae, K. pneumoniae, P. aeruginosa* and *Serratia marcescens*. Similarly, super infections (those caused by resistant pathogens) were more common with doripenem. Resistant organisms included *Candida* species, *Enterococcus* species, *E. coli, Myroides* species, *S. aureus* and *S. maltophilia*.

The most common adverse events with doripenem in the clinical trials were headache (10%), diarrhoea (9%) and nausea (8%). Occasionally more serious adverse events have occurred that were thought to be related to doripenem. These included atrial fibrillation, atrial flutter, acute renal failure, renal impairment, cholestasis, abnormal liver function test, convulsion and hypotension. Treatment was discontinued in 1 in every 1000 patients – reasons included nausea, diarrhoea, pruritus, vulvomycotic infection, increased hepatic enzymes and rash.

As with other carbapenems, doripenem may reduce sodium valproate concentrations in serum, so concentrations should be monitored. An alternative antibiotic or anticonvulsant may be needed if therapeutic doses of valproate cannot be maintained or if seizures occur. Probenecid reduces the renal clearance of doripenem therefore co-administration of these drugs is not recommended. Doripenem is contraindicated in patients who are allergic to penicillins and other beta lactam antibiotics.

Doripenem offers an alternative for patients with serious infections when other treatments have failed, however the approval of this drug is mainly based on data from non-inferiority trials.[4] As with the other carbapenems, bacterial resistance is a problem. Although *in vitro* studies show that doripenem has increased activity against *P. aeruginosa*, there are limited data from the trials to suggest this is also the case in infected patients.

T manufacturer provided only the product information

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Japanese encephalitis vaccine

Jespect (CSL)

0.5 mL suspension in a pre-filled syringe

Approved indication: prevention of Japanese encephalitis

Australian Medicines Handbook section 20.1

Japanese encephalitis is a viral infection transmitted by mosquitoes. Although most infections are asymptomatic, symptomatic infection is often serious and can lead to neurological sequelae or death. The virus has been found throughout Asia and Papua New Guinea and vaccination is indicated for adults who live in or travel to these endemic areas, or who work with the virus in laboratories.

Production of the currently approved vaccine for Japanese encephalitis has been discontinued because of safety concerns regarding hypersensitivity reactions. This was an inactivated vaccine made from Nakayama and SA_{14}-14-2 virus strains propagated in mouse brains. A new inactivated vaccine has been developed in which the virus (strain SA_{14}-14-2) is grown in

tissue culture using Vero cells and not in mice.

In a comparative study of the two vaccines, 863 adults received either two intramuscular injections of the Vero cell-derived vaccine (days 0 and 28) or three doses of the vaccine derived from infected mouse brains (days 0, 7 and 28). Efficacy was assessed by measuring titres of virus-specific antibody in serum. The ability of this antibody to neutralise virus was also measured. The seroconversion rate was the percentage of participants whose serum (diluted at least 1:10) reduced the ability of the SA_{14}-14-2 virus to infect a cell monolayer by 50%. Four weeks after the final injection, the seroconversion rate for the test vaccine was similar to that of the comparator (98% vs 95%), and mean antibody titres were twice as high as in the comparator group. (This analysis was done on the per-protocol population of 735 people).[1] In a long-term uncontrolled follow-up study, 83% of people who had received a course of the Vero-derived vaccine 12 months earlier (181 vaccinees) had seroconverted. Mean titres had dropped at this time point.[2]

Systemic adverse reactions to the vaccines were similar, with headache (26%), myalgia (21%), influenza-like illness (13%) and fatigue (13%) being most commonly reported in the Vero-derived vaccine group. Localised reactions to the Vero-derived vaccine were much lower than with the comparator. For instance, redness was reported by 1% of people given the Vero-derived vaccine compared to 11% of those given the comparator vaccine. Swelling, hardening and tenderness after injection were also less frequent.[1] Similar tolerability to the Vero-derived vaccine was found in a placebo-controlled safety trial of 2650 participants.[3]

Due to lack of data, this vaccine should not be given to pregnant or breastfeeding women unless it is clearly needed. Likewise, it is not known how safe or effective this vaccine is in children.

Co-administration with inactivated hepatitis A vaccine did not interfere with the immune response to the Vero-derived vaccine. If other vaccines are indicated, injections should be given in the opposite arm. Response may be reduced in people who are immunosuppressed.

The actual effectiveness of this new vaccine is unknown. However, it has been inferred from previous studies that if an individual seroconverts to produce virus-neutralising antibody they will be protected against infection. Based on seroconversion rates in the trials, the vaccine should protect most people from Japanese encephalitis for up to a year. It is not known if further vaccinations will be needed after this.

Another way to assess immunogenicity of the vaccine is to measure cell-mediated immunity (which involves T cells directly and not humoral antibody), an important defence against viruses. There are no data on this from the trials but studies are underway.

T T manufacturer provided additional useful information

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Sugammadex

Bridion (Schering Plough)

vials containing 100 mg/mL solution for injection

Approved indication: reversal of neuromuscular blockade by rocuronium or vecuronium

Australian Medicines Handbook section 2.4.4

Drugs that reverse neuromuscular blockade are used by anaesthetists at the end of surgery to accelerate recovery from drug-induced muscle relaxation. Sugammadex is a modified gamma cyclodextrin designed to selectively reverse the effects of the neuromuscular blockers rocuronium and vecuronium. It works by forming a complex with these drugs, reducing their availability to bind to nicotinic receptors in the neuromuscular junction. There are no safety and efficacy data to support the use of sugammadex for reversing other neuromuscular blockers including suxamethonium, and benzylisoquinolium compounds such as atracurium and cisatracurium. Similarly, sugammadex should not be used to reverse pancuronium-induced blockade.

Until now, cholinesterase inhibitors such as neostigmine and edrophonium have been used to reverse neuromuscular blockade after surgery. However, these drugs have a relatively slow onset and have adverse effects associated with stimulation of muscarinic receptors. In addition, neostigmine cannot be used to reverse profound blockade.

The dose of sugammadex depends on the degree of neuromuscular blockade required. In a comparative trial of 182 randomised patients, sugammadex (4 mg/kg) was more effective than neostigmine (70 microgram/kg) at reversing profound neuromuscular blockade induced by rocuronium or vecuronium. The mean time to recovery of muscle function (measured using an acceleromyograph) was three minutes after the sugammadex injection compared to 50 minutes after neostigmine.[1,2] Sugammadex (2 mg/kg) was also quicker than neostigmine (50 microgram/kg) at reversing moderate neuromuscular blockade (mean recovery times of 1–2 mins vs 16–18 mins) in a trial of 189 patients.

In situations where immediate reversal of rocuronium-induced blockade is required, the recommended dose is 16 mg/kg of sugammadex three minutes after rocuronium administration. This recommendation is based on a trial comparing sugammadex for immediate reversal of rocuronium-induced blockade with spontaneous recovery of 110 patients given the short-duration muscle relaxant suxamethonium. Mean recovery times were quicker with sugammadex than with the comparator (4 mins vs 7 mins). There are no clinical data to recommend sugammadex for immediate reversal of vecuronium-induced blockade.[3]

Following intravenous administration, sugammadex has an elimination half-life of 2.2 hours. This is increased in elderly patients and decreased in children. After injection, most of the sugammadex dose is excreted unchanged in the urine, so its use in people with severe renal impairment is not recommended. Longer recovery times may be observed in older patients as well as people with cardiovascular disease, oedema or severe hepatic impairment.[3]

If re-administration of rocuronium or vecuronium is required after reversal with sugammadex, a waiting period is recommended. The duration depends on the dose of sugammadex, the dose of rocuronium or vecuronium, and the patient's renal function.

The most common adverse effect of sugammadex is a disturbance in taste (metallic or bitter taste), which was reported by 12% of patients in a dose escalation trial (mainly after a higher dose of 32 mg/kg). Recurrent blockade has occurred with sugammadex (2% of patients), however this was mostly associated with a suboptimal dose of sugammadex (less than 2 mg/kg). Anaesthetic complications such as body movement, coughing or grimacing during the anaesthetic (which are signs of restoration of neuromuscular function) were thought to be related to sugammadex treatment in about 1% of patients. Allergic reactions, such as flushing or erythematous rash, have been observed with sugammadex.

Sugammadex should not be used in children less than two years. In older children and adolescents, there are limited efficacy and safety data to support its routine use. Immediate reversal in children has not been assessed.

Although no direct drug interactions are expected with sugammadex, drugs interacting with vecuronium or rocuronium could potentially affect the efficacy of sugammadex. Toremifene, fusidic acid and flucloxacillin can displace vecuronium or rocuronium from the complex with sugammadex. This would potentially delay recovery time. High doses of flucloxacillin (500 mg or more) should be avoided in the postoperative period.

Prescribers need to be aware that sugammadex may decrease progestogen concentrations, similar to the decrease observed after missing a daily dose of an oral contraceptive. Women on the pill should refer to the missed dose advice for their contraceptive. Likewise, women using non-oral hormonal contraceptives, such as depot formulations, should be advised to use additional contraception for the next seven days.

Sugammadex may affect haemostasis by interfering with the coagulation cascade. Patients with pre-existing coagulation abnormalities should therefore be monitored for activated partial thromboplastin time, prothrombin time and INR after receiving sugammadex.

Prolongation of the QT_c interval has been noted in some patients receiving sugammadex, however torsades des pointes has not occurred. QT_c prolongation is a concern in situations where sugammadex is given with other drugs that affect the QT interval such as the anaesthetics sevoflurane and propofol.

Sugammadex is the first selective relaxant binding agent. It rapidly reverses neuromuscular block induced by rocuronium or vecuronium regardless of the depth of the block. However, recurrence of neuromuscular blockade has been reported with this drug so close monitoring of respiratory function remains vital during the recovery period. This drug has not been assessed in intensive care units.

T manufacturer provided only the product information

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The T-score (T) is explained in 'New drugs: transparency' on pages 80–1 of this issue.

* 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).