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.

Alfuzosin

Xatral SR (Sanofi-Aventis)

10 mg prolonged-release tablets

Approved indication: benign prostatic hyperplasia

Australian Medicines Handbook section 13.2.1

Alpha$_1$ adrenergic blocking drugs such as prazosin can be used in the treatment of benign prostatic hyperplasia. They work by relaxing the smooth muscle of the bladder and prostate. Prescribers can now consider using alfuzosin as an alternative to prazosin, tamsulosin and terazosin in patients who have symptoms of benign prostatic hyperplasia.

Early studies used 2.5 mg and 5 mg tablets, but the manufacturer is now marketing a 10 mg prolonged-release formulation. The tablet is taken daily after a meal as bioavailability is reduced if it is taken on an empty stomach. The half-life is about nine hours and only slightly increases with age. Most of a dose is metabolised, then excreted in the faeces. As this metabolism involves cytochrome P450 3A4, alfuzosin may interact with inhibitors of this enzyme such as the imidazole antifungals. Hepatic insufficiency is a contraindication.

In the early 1990s, 5 mg sustained-release tablets were studied for three months in 390 men with symptomatic benign prostatic hyperplasia. A twice-daily dose significantly reduced symptom scores and the urine flow rate improved significantly more with alfuzosin than with placebo. The amount of residual urine was also significantly reduced.[1]

A pooled analysis of three subsequent studies of a 10 mg sustained-release formulation reported results after 12 weeks of treatment. Compared with 482 men given placebo, the 473 who were randomised to receive alfuzosin had a significant improvement in lower urinary tract symptoms. The absolute decrease in the 35-point international prostate symptom score (IPSS) was 4.2 points with placebo and 6 points with alfuzosin. There was also a significant improvement in the urinary peak flow rate.[2]

In an open-label extension of one of these studies, 310 men took alfuzosin 10 mg for nine months. The improvements in the IPSS and urine flow were maintained.[3]

Another one of the trials included 158 patients taking 0.4 mg tamsulosin, which is also an alpha$_1$ adrenergic blocker. After 12 weeks their IPSS had reduced by 6.5 points which was identical to the reduction seen in the 154 patients who were randomised to take alfuzosin 10 mg. These changes were significantly greater than the 4.6 point reduction seen in the 153 patients who took placebo.[4]

When alfuzosin was compared with doxazosin in 210 men, both drugs significantly improved urinary flow rates over 14 weeks. The reduction in the IPSS was significantly greater with doxazosin (9.2 points) than with alfuzosin (7.5 points). The residual volume of urine was also significantly less with doxazosin. However, this trial used the 2.5 mg and 5 mg formulations of alfuzosin and the mean dose was less than 10 mg, which is now the recommended dose.[5]

Alfuzosin has also been studied as an adjunctive treatment in the management of acute urinary retention. Following catheterisation, 238 men were given daily alfuzosin and 122 were given a placebo. The catheters were removed after two doses and treatment continued for the day after removal. A return to satisfactory micturition was achieved by 61.9% of the alfuzosin group and 47.9% of the placebo group. A group of 165 responders was then randomised to take alfuzosin or a placebo for six months. During this period surgery for prostatic hyperplasia was needed by 17.1% of the alfuzosin group and 24.1% of the placebo group. Approximately 14 men would need to be treated for six months for one to avoid surgery.[6]

As alpha$_1$ adrenergic blocking drugs cause vasodilation, adverse effects such as postural hypotension may be expected. Patients may complain of dizziness or faintness. Particular caution is required if alfuzosin is prescribed for patients who are taking antihypertensive drugs.

In the pooled analysis 9.5% of patients taking alfuzosin stopped treatment compared with 8.7% of the placebo group. Symptoms associated with vasodilation occurred in 6.6% of elderly patients and 8.3% of those with hypertension.[2] In a meta-analysis alfuzosin caused significantly more dizziness, hypotension or syncope than placebo.[7]

Alfuzosin has been available overseas for many years. No specific safety problems have emerged, but there could be a risk of the 'floppy iris syndrome', a complication in cataract surgery, which has been reported with similar drugs such as tamsulosin.

Although alfuzosin has some statistically significant effects, their clinical relevance is less clear. As the IPSS has to change by at least three points to be noticed, the benefit of alfuzosin over placebo is modest. In the pooled analysis, placebo increased the maximum urinary flow by 12.5%, while alfuzosin increased it by

26.1%. However, the absolute increases were 1.1 mL/second and 2.3 mL/second. The difference, of 1.2 mL/second, may not be clinically important.[2]

A meta-analysis has evaluated the efficacy of all the alpha$_1$ adrenergic blocking drugs used to treat the symptoms of benign prostatic hyperplasia. It found no difference between the drugs. They all improve symptom scores and peak urinary flow.[7]

T T manufacturer provided additional useful information

References *

1. Buzelin JM, Roth S, Geffriaud-Ricouard C, Delauche-Cavallier MC; ALGEBI Study Group. Efficacy and safety of sustained-release alfuzosin 5 mg in patients with benign prostatic hyperplasia. Eur Urol 1997;31:190-8.
2. Roehrborn CG, van Kerrebroeck P, Nordling J. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. BJU Int 2003;92:257-61.
3. van Kerrebroeck P, Jardin A, van Cangh P, Laval KU; ALFORTI Study Group. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. Eur Urol 2002;41:54-61.
4. Nordling J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. BJU Int 2005;95:1006-12.
5. De Reijke TM, Klarskov P. Comparative efficacy of two α_1-adrenoreceptor antagonists, doxazosin and alfuzosin, in patients with lower urinary tract symptoms from benign prostatic enlargement. BJU Int 2004;93:757-62.
6. McNeill SA, Hargreave TB, Roehrborn CG; ALFAUR Study Group. Alfuzosin 10 mg once daily in the management of acute urinary retention: results of a double-blind placebo-controlled study. Urology 2005;65:83-90.
7. Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of α-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract 2008;62:1547-59.

Clofarabine

Evoltra (Hospira)

vials containing 20 mg/20 mL

Approved indication: paediatric acute lymphocytic leukaemia

Australian Medicines Handbook section 14.1.3

Acute lymphocytic leukaemia is the most common childhood malignancy. Although chemotherapy has improved survival, many children have a high risk of relapse. As chemotherapy can be ineffective in relapsed disease there is a need for new therapies.

Clofarabine is a purine nucleoside analogue. It has structural similarities to the purine antagonists cladribine and fludarabine. After dilution and slow intravenous infusion, clofarabine is converted intracellularly to a metabolite which inhibits DNA synthesis and induces apoptosis. There is little hepatic metabolism with 50–60% of the dose being excreted unchanged in the urine. The terminal half-life is approximately five hours.

The approval of clofarabine is based on a phase II study of 61 people whose acute lymphocytic leukaemia was refractory or had relapsed at least twice. Their ages ranged from 1 to 20 years with a median of 12 years. Clofarabine was infused for five consecutive days every 2–6 weeks for up to 12 cycles depending on the toxicity of the treatment. As judged by blood counts and bone marrow aspirates, 20% of patients had a complete remission and 10% had a partial remission. Some of these remissions were in patients whose leukaemia had been refractory to previous treatment.[1]

Clofarabine is an antimetabolite so it frequently causes serious adverse effects. In the first two treatment cycles 72% of the patients had severe febrile neutropenia.[1] Multi-organ failure, haematemesis, hypotension, jaundice and septic shock occur commonly. A rapid reduction in leukaemia cells can cause cytokine release and tumour lysis syndrome, so intravenous fluids are recommended for the five days of each treatment cycle. Most patients experience nausea, vomiting and diarrhoea so antiemetic drugs should be considered. Skin reactions, such as palmar-plantar erythrodysaesthesia syndrome, are very common. During the phase II trial, 25% of the patients died within 30 days of treatment or as a result of a drug-related adverse effect.[1]

The median survival time for the patients in the trial was 13 weeks.[1] Survival improves in patients who respond, but this outcome may be confounded because these patients may subsequently have bone marrow transplantation. Median overall survival is 63 weeks in patients who respond and may be longer in those who have a transplant. Most of the responses to clofarabine occur in the first two treatment cycles. Patients were only able to complete a median of two cycles in the trial, so it may not be worthwhile persisting with treatment in those who do not respond by then. In view of the limited information about clofarabine, its use has been restricted to children with relapsed or refractory disease who have already received two previous treatment regimens.

T manufacturer provided only the product information

Reference *†

1. Jeha S, Gaynon PS, Razzouk BI, Franklin J, Kadota R, Shen V, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. J Clin Oncol 2006;24:1917-23.

Melatonin

Circadin (Sigma)

2 mg prolonged-release tablets

Approved indication: primary insomnia

Australian Medicines Handbook section 18.4

Melatonin is a hormone which is secreted by the pineal gland at night-time. Its secretion is part of the normal circadian rhythm and promotes sleep. This resulted in a theory that low concentrations of melatonin may be associated with difficulty sleeping.

A study of 59 volunteers and 517 patients with insomnia found that the patients had lower urinary concentrations of a melatonin metabolite. When 396 of the patients were given an evening dose of melatonin, those with lower concentrations of the metabolite had a greater clinical response than those with higher concentrations. They had a better quality of sleep and they found it easier to get to sleep. The following morning they were more alert than the patients with higher urinary concentrations.[1]

Several randomised controlled trials then looked at using melatonin to treat primary sleep disorders. A meta-analysis of 16 of these studies found that melatonin was as well tolerated as placebo, but was not very efficacious. Patients given melatonin fell asleep 12 minutes earlier than those given a placebo. The effect was greater (39 minutes) in the small sub-group with delayed sleep phase syndrome. Melatonin did not increase sleep efficiency (the proportion of time in bed spent asleep) significantly more than placebo.[2]

Another meta-analysis looked at sleep disorders secondary to other conditions or sleep restriction, for example jet lag. It found no evidence that melatonin was of any benefit.[3]

The meta-analysis of primary insomnia concluded that larger controlled trials were needed.[2] One subsequent trial in general practice randomised 170 patients, over the age of 55 years, with primary insomnia to take 2 mg modified-release melatonin or placebo. After three weeks there was no significant difference in getting to sleep, but sleep quality and alertness the next day were significantly improved with melatonin.[4]

A similar trial in general practice randomised 177 patients to take 2 mg modified-release melatonin and 177 to take a placebo. After three weeks, patients given melatonin fell asleep approximately nine minutes faster than the placebo group. They also had greater improvements in their quality of sleep and morning alertness, however total sleep time was not significantly improved.[5]

Adverse events occurred in 37% of the patients given melatonin and 32% of the patients given placebo. The most frequently reported symptoms were headache, back pain, asthenia and pharyngitis.

Melatonin undergoes significant first pass metabolism and most of the dose is excreted in the urine as metabolites. This metabolism involves cytochrome P450 1A1, 1A2 and possibly 2C19. It may be inhibited by drugs such as cimetidine, fluvoxamine, oestrogen and the quinolones, and induced by smoking and drugs such as carbamazepine and rifampicin. Melatonin is not recommended for patients with liver impairment and the effect of renal impairment is unknown. As the half-life of melatonin is less than an hour a modified-release formulation is needed. After a meal it takes three hours to reach the maximum plasma concentration, so it is recommended that the modified-release tablet is taken one or two hours before bedtime and after food. Patients should not drink alcohol with melatonin, as alcohol may cause the immediate release of the drug from the modified-release formulation.

There appear to have been no direct comparisons with benzodiazepines, but the results of a separate placebo-controlled trial with zolpidem have been used to assess the relative efficacy of melatonin. Overall patients given zolpidem fall asleep sooner than those given melatonin, but both drugs improve sleep quality. Melatonin should not be used in combination with other hypnotics. Stopping melatonin does not appear to cause more withdrawal symptoms than placebo,[4] but its use is restricted to a maximum of three weeks. It can only be prescribed to patients with primary insomnia over the age of 55 years. Many of these patients will be disappointed with the effect, as only about 30% respond to treatment. When the placebo effect is discounted, nine people would need to be treated for three weeks for one person to have improved sleep quality and to function better the next morning.[5]

T T manufacturer provided additional useful information

References †A

1. Leger D, Laudon M, Zisapel N. Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. Am J Med 2004;116:91-5.
2. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders: a meta-analysis. J Gen Intern Med 2005;20:1151-8.
3. Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ doi:10.1136/bmj.38731.532766.F6 (published 2006 Feb 10)
4. Lemoine P, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. J Sleep Res 2007;16:372-80.
5. Wade AG, Ford I, Crawford G, McMahon AD, Nir T, Laudon M, et al. Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness outcomes. Curr Med Res Opin 2007;23:2597-605.

Nebivolol

Nebilet (CSL)

1.25 mg, 5 mg and 10 mg tablets

Approved indication: hypertension, chronic heart failure

Australian Medicines Handbook section 6.4.3

Nebivolol is indicated for the treatment of essential hypertension (no age limit), and for stable chronic heart failure in combination with conventional therapies for patients aged 70 or older. It works by blocking the $beta_1$ adrenergic receptor, and has mild vasodilatory properties mediated through nitric oxide release. At doses up to 10 mg, it is selective for the $beta_1$ adrenergic receptor, but at higher doses (and in poor metabolisers) it inhibits both $beta_1$ and $beta_2$ adrenergic receptors.

Peak plasma concentrations of this drug are reached 1.5–4 hours after oral administration. It is metabolised by cytochrome P450 2D6 and its elimination half-life is around 10 hours in most people (fast metabolisers), but 3–5 times longer in people who are slow metabolisers. Metabolites are excreted in urine and faeces in varying proportions depending on the individual's metabolism. As there are variations in the metabolism of nebivolol, the dose should be adjusted according to individual needs. Poor metabolisers may require a lower dose.

Once-daily nebivolol (1.25–40 mg) has been shown to reduce blood pressure in patients with mild–moderate hypertension in a number of placebo-controlled trials.[1,2] A nine-month extension of these trials compared nebivolol monotherapy to nebivolol given with other antihypertensive treatments in 845 people. (Of these patients, 81 had previously received placebo and 764 had received nebivolol.) Patients were given nebivolol monotherapy (5–20 mg). If they did not have an adequate response to this, a diuretic, calcium channel blocker (amlodipine) or another antihypertensive drug was added to their treatment. By the end of the study, mean diastolic and systolic blood pressures had decreased by 15 mmHg and 14.8 mmHg in the nebivolol group (606 patients) and by 12 mmHg and 16.2 mmHg in the nebivolol plus diuretic group (206 patients) from baseline of the original studies. There were too few patients in the other groups to conclude whether treatment had worked.[3]

In a meta-analysis of hypertension drugs, response rates to nebivolol (5 mg daily) were similar to other beta blockers, calcium channel antagonists and the angiotensin receptor antagonist losartan. Response rates to nebivolol were higher than for angiotensin converting enzyme inhibitors.[4]

In one of the original hypertension trials that tested nebivolol (1.25–40 mg) for 12 weeks, headache (6–9%), fatigue (1.2–4.8%) and dizziness (1–9%) were commonly reported adverse events. Patients treated with the higher doses of nebivolol (20 mg and 40 mg) had significantly more adverse events, possibly because nebivolol becomes less selective at higher doses. There were two serious adverse events that were thought to be possibly related to nebivolol (20 mg and 40 mg dose). Both were abnormal ECG readings which resolved spontaneously without treatment being interrupted. High-density lipoprotein cholesterol decreased significantly with increasing nebivolol dose, and increases in serum uric acid and phosphorus were observed at doses of 5 mg and above.[1] In the extension study, there were three patients with serious adverse events that were thought to be related to the study drug. These included right upper quadrant pain, bradycardia and peripheral oedema, and sexual dysfunction. Obese patients (≥ 30 kg/m^2) tended to have more adverse events than patients who were not obese.[3] In the meta-analysis, adverse event rates for nebivolol were lower than for other beta blockers, calcium channel antagonists and losartan. The tolerability of nebivolol and ACE inhibitors was similar.[4]

In Australia, nebivolol has also been approved as an add-on treatment for heart failure in older patients. This is based on the SENIORS trial in 2128 patients aged 70 years and over with heart failure. This was a *post hoc* analysis and patients were not randomised to receive different doses of nebivolol. They were started on placebo, or a low dose of nebivolol which was gradually increased to 10 mg, if tolerated, over a maximum of 16 weeks. The target dose was reached by two-thirds of the patients in the nebivolol group and was associated with a significant reduction (relative risk reduction of 4.2%) in the composite end point of all-cause mortality or hospitalisation (due to a cardiovascular event), compared to placebo. However, nebivolol did not significantly reduce all-cause mortality alone. There was no significant benefit with low-dose nebivolol and patients who could not tolerate it had a higher risk of death or hospitalisation than those on placebo. It is not clear how nebivolol compares to other beta blockers in this population.[5]

In the heart failure trial, around 20% of patients had aggravated cardiac failure regardless of whether they were taking placebo or nebivolol. However, bradycardia was considerably more common with nebivolol than with placebo (11% vs 2.5% of patients). Dizziness was reported by 14% of patients in the nebivolol group and 13% in the placebo group.[5]

Spontaneous adverse events reported overseas with this drug have included abnormal liver function, acute pulmonary oedema, acute renal failure, myocardial infarction, Raynaud's phenomenon, thrombocytopenia and skin disorders including rashes. However, their frequency and causal relationship with nebivolol is not known.

Nebivolol has the potential to interact with many drugs, therefore it is important to read the product information before prescribing it. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, quinidine, thioridazine and cimetidine, are likely to increase nebivolol concentrations so patients' blood pressure should be monitored closely in case dose adjustment is required. Nebivolol is not recommended with the calcium channel

antagonists verapamil and diltiazem, class I antiarrhythmic drugs (flecainide, disopyramide, lignocaine, mexiletine) and with centrally-acting antihypertensives (clonidine, moxonidine, methyldopa). Nebivolol should not be used with other beta blockers, including eye drops.

As beta blockade can depress myocardial contractility, it can worsen heart failure so nebivolol should not be given to patients with acute heart failure or untreated congestive heart failure. Other contraindications include sick sinus syndrome (without pacemaker), severe bradycardia, heartblock (more than first degree), hypotension, severe circulatory disturbances, metabolic acidosis and history of bronchospasm.

As with other beta blockers, patients should be warned against stopping nebivolol abruptly as this can exacerbate angina and precipitate myocardial infarction and ventricular arrhythmias.

When used for hypertension, dose adjustment is required in patients with renal impairment. There are no data on the use of nebivolol in patients receiving dialysis. For chronic heart failure, dose adjustment is not needed in mild to moderate renal insufficiency. Nebivolol is not recommended for patients with severe renal impairment. This drug is contraindicated in patients with hepatic impairment.

Nebivolol seems to be as effective as other antihypertensive drugs at lowering blood pressure and it benefits some patients with heart failure. However, until long-term data on its clinical use are available, it is probably better to continue to use the more established beta blockers.

T manufacturer provided only the product information

References *

1. Weiss RJ, Weber MA, Carr AA, Sullivan WA. A randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy and safety of nebivolol, a novel β-blocker, in patients with mild to moderate hypertension. J Clin Hypertens 2007;9:667-76.
2. Saunders E, Smith WB, DeSalvo KB, Sullivan WA. The efficacy and tolerability of nebivolol in hypertensive African American patients. J Clin Hypertens 2007;9:866-75.
3. Papademetriou V. Comparison of nebivolol monotherapy versus nebivolol in combination with other antihypertensive therapies for the treatment of hypertension. Am J Cardiol 2009;103:273-8.
4. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs 2008;8:35-44.
5. Dobre D, van Veldhuisen DJ, Mordenti G, Vintila M, Haaijer-Ruskamp FM, Coats AJS, et al. Tolerability and dose-related effects of nebivolol in elderly patients with heart failure: data from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) trial. Am Heart J 2007;154:109-15.

Pneumococcal polysaccharide conjugate vaccine

Synflorix (GlaxoSmithKline)

0.5 mL suspension in pre-filled syringes

Approved indication: prevention of *Streptococcus pneumoniae* infections

Australian Medicines Handbook section 20.1

This vaccine is indicated for the prevention of invasive pneumococcal disease (including pneumonia and acute otitis media) in children aged 6 weeks to 2 years. The current conjugate vaccine for this age group contains polysaccharides from seven *S. pneumoniae* serotypes (4, 6B, 9V, 14, 18C, 19F and 23F), whereas this new vaccine contains an additional three serotypes (1, 5 and 7F). Most of the polysaccharides in the new vaccine are conjugated to protein D (a conserved *Haemophilus influenzae* surface protein) rather than diphtheria toxoid which is used in the current vaccine.

The World Health Organization (WHO) has recommended that approval of pneumococcal vaccines for invasive disease can be based on immunogenicity data alone rather than efficacy trials. New vaccines should be non-inferior to the current seven-valent pneumococcal vaccine. Based on efficacy studies, the WHO has defined an antibody threshold which correlates to protection. This antibody must also be able to opsonise *S. pneumoniae* and promote phagocytosis by immune cells.

The new vaccine was found to be non-inferior to the seven-valent vaccine in an immunogenicity trial of 1650 babies. They were given three intramuscular doses before the age of six months and antibody titres in sera were measured a month after the last injection. An increase in titres was seen after a booster at 12 months indicating that babies had developed immune memory to the polysaccharides.[1] (Antibody data for serotypes 1, 5 and 7F could not be compared to the seven-valent vaccine.)

Protection against acute otitis media is more difficult to achieve than protection against invasive infections. In a trial of 4968 babies, an eleven-valent experimental vaccine containing the ten serotypes of this new vaccine conjugated to protein D was compared to a control vaccine for hepatitis A. After vaccination (at 3, 4, 5 and 12–15 months), efficacy against acute otitis media during the follow-up period was 58% for vaccine serotypes, and efficacy against ear infections caused by non-typeable *H. influenzae* was 35%.[2] Although not significant, the incidence of recurrent ear infections and the number of children needing grommets were less in the pneumococcal vaccine group.

When given at the same time, the pneumococcal vaccine did not affect the immunogenicity of a combined vaccine against hepatitis B, diphtheria, tetanus and acellular pertussis, *H. influenzae* type b and poliomyelitis.[2] About 40% of infants had injection-site reactions after the vaccination. Irritability and mild fever were also common and can be treated with an antipyretic drug.[3]

The vaccine should be given by intramuscular injection, so caution is urged in children with thrombocytopenia or coagulation disorders because of the risk of bleeding. The safety and efficacy of this vaccine has not been established in children who have an increased risk of pneumococcal infections such as those with sickle cell disease, splenic dysfunction, HIV, malignancy or nephrotic syndrome.

The vaccine should not be withheld or delayed in premature babies, but their respiration should be monitored for 2–3 days after the first vaccination. Antibody responses in immunocompromised children may be reduced.

This vaccine should be given to infants at 2, 4 and 6 months (in the thigh), with a booster at 12 months (in the upper arm). As with the current pneumococcal vaccine, it can be co-administered with other vaccines recommended in the Australian immunisation schedule.

Based on immunological data, this vaccine should protect most babies from invasive pneumococcal disease such as pneumonia, bacteraemia and meningitis caused by the vaccine serotypes. The vaccine was efficacious against acute otitis media, but it is not known if it will be any better than the current vaccine, or how it will perform in communities where uncommon serotypes have become more prevalent.[4] Because this vaccine contains protein D from *H. influenzae*, it should offer some protection against ear infections caused by non-typeable *H. influenzae*.

T T manufacturer provided additional useful information

References

1. Vesikari T, Wysocki J, Chevallier B, Karvonen A, Czajka H, Arsène JP, et al. Immunogenicity of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Paediatr Infect Dis J 2009;28:S66-S76.
2. Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study. Lancet 2006;367:740-8.
3. Prymula R, Chlibek R, Splino M, Kaliskova E, Kohl I, Lommel P, et al. Safety of an 11-valent pneumococcal vaccine conjugated to non-typeable *Haemophilus influenzae*-derived protein D in the first 2 years of life and immunogenicity of the co-administered hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, *Haemophilus influenzae* type b and control hepatitis A vaccines. Vaccine 2008;26:4563-70.
4. Marsh RL, Smith-Vaughan H, Beissbarth J, Hare K, Kennedy M, Wigger C, et al. Molecular characterisation of pneumococcal serotype 16F: established predominant carriage and otitis media serotype in the 7vPCV era. Vaccine 2007;25:2434-6.

Rizatriptan benzoate

Maxalt (MSD)

10 mg wafers

Approved indication: migraine

Australian Medicines Handbook section 16.3.2

It is almost twenty years since the launch of sumatriptan, the first serotonin ($5HT_1$) receptor agonist. While sumatriptan benefited many patients with migraine, it was not ideal because of its low oral bioavailability and short half-life. This led to the development of other 'triptans'.

Rizatriptan is a serotonergic agonist which mainly acts on $5HT_{1B}$ and $5HT_{1D}$ receptors. This constricts the extracerebral and intracranial arteries which become dilated during an attack of migraine.

The wafers have a bioavailability of 45%. Food may affect absorption, but appears to have no effect on efficacy. Rizatriptan is metabolised by monoamine oxidase so it should not be prescribed for patients who have taken monoamine oxidase inhibitors in the previous two weeks. Plasma concentrations are also increased by propranolol, so a lower dose of rizatriptan is recommended in patients taking this beta blocker. Most of the metabolites of rizatriptan are excreted in the urine. The half-life is similar to that of sumatriptan (2–3 hours).

An early dose-ranging study compared rizatriptan with sumatriptan and placebo. The study assessed 449 patients and found that headache was reduced within two hours in 18% of the placebo group, 46% of the sumatriptan group and 52% of the patients who took 10 mg rizatriptan. This dose relieved pain completely in 26% of patients compared with 22% of the sumatriptan group and 3% of the placebo group. The headache returned in 41% of the patients taking rizatriptan 10 mg and 41% of the sumatriptan group.[1] If the headache returns, patients can take another dose of rizatriptan, but doses must be at least two hours apart and not exceed 30 mg in 24 hours.

As rizatriptan has been marketed overseas for several years, there are many studies of its use in migraine, however only some of these studied the wafer formulation. Two hours after a dose, 66% of patients with moderate to severe headache will respond to a wafer and 47% will respond to a placebo.

A meta-analysis found more patients responded to a 10 mg dose of rizatriptan than to a 100 mg dose of sumatriptan. Significantly more were pain free after two hours, but the headache was more likely to return within 24 hours in patients taking rizatriptan.[2]

The meta-analysis was used to calculate the number of patients who need to be treated for 100 to have sustained relief for 24 hours. These figures were 490 for sumatriptan 100 mg, and 458 for rizatriptan 10 mg. To treat 100 patients successfully required a total of 534 doses of sumatriptan 100 mg, or 516 doses of rizatriptan 10 mg.[3]

Rizatriptan has also been compared with other analgesics for migraine. In one placebo-controlled study 200 patients were randomised to take rizatriptan tablets, paracetamol, or both. After two hours 90% of the patients taking both drugs had responded compared with 77% of the rizatriptan group, 70% of the paracetamol group and 46% of the placebo group. Over 24 hours 62% of the patients taking both drugs had sustained relief, but this was not statistically superior to the 53% of the rizatriptan group and the 42% of the paracetamol group.[4]

Adverse events occur at a similar frequency to reactions to sumatriptan 100 mg.[2] Common adverse effects of rizatriptan include tiredness and dizziness. Like other drugs in the class, rizatriptan can cause pain in the chest and neck. It is contraindicated in ischaemic heart disease or uncontrolled hypertension. There is a risk of serotonin syndrome, particularly in patients taking serotonin reuptake inhibitors. Ergot alkaloids should not be used within six hours of rizatriptan.

T T manufacturer provided additional useful information

References *

1. Visser WH, Terwindt GM, Reines SA, Jiang K, Lines CR, Ferrari MD; Dutch/US Rizatriptan Study Group. Rizatriptan vs sumatriptan in the acute treatment of migraine. A placebo-controlled, dose-ranging study. Arch Neurol 1996;53:1132-7.
2. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001;358:1668-75.
3. Mullins CD, Weis KA, Perfetto EM, Subedi PR, Healey PJ. Triptans for migraine therapy: a comparison based on number needed to treat and doses needed to treat. J Manag Care Pharm 2005;11:394-402.
4. Freitag F, Diamond M, Diamond S, Janssen I, Rodgers A, Skobieranda F. Efficacy and tolerability of coadministration of rizatriptan and acetaminophen vs rizatriptan or acetaminophen alone for acute migraine treatment. Headache 2008;48:921-30.

Ustekinumab

Stelara (Janssen-Cilag)

45 mg/0.5 mL solution for injection

Approved indication: psoriasis

Australian Medicines Handbook section 8.2.1

Ustekinumab, a humanised monoclonal antibody, is a new treatment for moderate to severe psoriasis (see 'Treatments for psoriasis', Aust Prescr 2009;32:14-8). It suppresses the immune system by blocking the inflammatory actions of interleukin (IL)-12 and IL-23, which contribute to the symptoms of psoriasis.

In a placebo-controlled study of 320 patients, ustekinumab improved symptoms of moderate to severe psoriasis in a dose-dependent manner.[1] Ustekinumab was then investigated in two crossover trials involving 1996 patients (PHOENIX 1 and PHOENIX 2). In both trials, patients were randomised (1:1:1) to receive ustekinumab 45 mg or 90 mg subcutaneously (at 0, 4 and then every 12 weeks), or placebo (at 0 and 4 weeks). After 4 weeks the patients in the placebo group crossed over to receive ustekinumab 45 mg or 90 mg (at 12 and 16 weeks and then every 12 weeks after that). The primary end point of the trials was the proportion of patients whose symptoms had improved by 75% after 12 weeks of treatment. Overall, significantly more patients in the ustekinumab groups reached this end point than in the placebo groups (67% with 45 mg and 71% (66–76%) with 90 mg vs 3% for placebo). These responses were maintained for up to a year in patients who continued treatment. After patients taking placebo crossed over to receive ustekinumab, a similar pattern of improvement was seen.[2,3] A subgroup analysis of the trials indicated that the efficacy of ustekinumab was slightly lower in obese patients and those aged 65 years or over.

In the PHOENIX 2 trial, patients who had partially responded after seven months of treatment (50–75% improvement in symptoms) were re-randomised to receive ustekinumab every eight weeks or to continue with the 12-week schedule. After a year, more patients receiving the 90 mg intensified dose responded to treatment than those receiving the original 12-week dosing (69% vs 33%). In contrast, patients did not respond to intensification of the 45 mg dose.[3]

Ustekinumab has been compared to etanercept, another psoriasis drug, in a trial of 855 patients. After 12 weeks of treatment, both doses of ustekinumab – 45 mg or 90 mg – seemed to be more effective than etanercept 50 mg given twice weekly. Of the patients, 72% and 65% receiving ustekinumab had improved symptoms compared to only 57% with etanercept. Adding etanercept to ustekinumab treatment did not improve response rates further. The trial is ongoing and will assess the effect of interrupting and restarting therapy on patients' symptoms.

In the PHOENIX trials, adverse events were similar between treatment and placebo groups with the most common complaints being upper respiratory tract infections, headache and arthralgia. Serious adverse effects with ustekinumab 45 mg included angina, stroke, hypertension, intervertebral disc protrusion, dactylitis, clavicular fracture, sciatica and nephrolithiasis. With the 90 mg dose, there was one sudden cardiac death in a 33-year-old patient. This was thought to be related to dilated cardiomyopathy. Other events included cellulitis, benign meningioma, transient palpitations and ventricular extrasystoles, and coronary artery disease requiring surgery. There were two serious infections with ustekinumab 90 mg (cellulitis and herpes zoster) and one basal cell carcinoma.[2,3] Depression was a common adverse event.

After a year of treatment, some patients had developed antibodies to ustekinumab. This was more common in patients who had only partially responded to treatment compared to those who had had a better response (12% vs 2%).[3]

Because of its immunosuppressant effects, ustekinumab is contraindicated in patients with clinically important active infections, chronic infections or a history of recurrent infections. There is a risk that latent infections may reactivate so patients should be assessed for tuberculosis and given appropriate treatment if necessary before starting ustekinumab. Live vaccines such as BCG (Bacillus Calmette-Guérin) should not be given. As with other immunosuppressants, ustekinumab may increase the risk of malignancy. It should not be given with other systemic treatments for psoriasis, or with phototherapy.

When ustekinumab is given at 0 and 4 weeks and then every 12 weeks, steady-state serum concentrations are achieved by week 28. If a patient has not responded by this time, treatment should be stopped. Ustekinumab has a long half-life (approximately three weeks) and due to the mechanism of action, its effects may last for several months.

Ustekinumab appears to be effective for psoriasis, and will probably prove popular with patients since injections are only needed every 12 weeks. However, because of the increased risk of serious adverse effects, ustekinumab is only indicated for patients who have not responded to other systemic treatments or cannot tolerate them.

[X] manufacturer did not respond to request for data

References

1. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007;356:580-92.
2. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74.
3. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84.

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).

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. False
2. False
3. False
4. False

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge. Readers can receive a **new issue email alert** showing the contents of the current issue.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list contact the *Australian Prescriber* Mailing Service.

Tick ✓ whichever of the following apply:

I have access to the *Australian Prescriber* website on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

☐ Change my address

☐ Send me the available back issues

Name: .....

Ref no.: .....
(on the address sheet above name)

Address: .....

.....

Profession: .....
(general practitioner, resident, etc.)

Postal: *Australian Prescriber* Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

Online: www.australianprescriber.com

Editorial office

For general correspondence such as Letters to the Editor, contact the Editor.

Telephone: (02) 6202 3100

Fax: (02) 6282 6855

Postal: The Editor, *Australian Prescriber*
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

Email: info@australianprescriber.com

Website: www.australianprescriber.com