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.

Desvenlafaxine succinate

Pristiq (Wyeth)

50 mg and 100 mg extended release tablets

Approved indication: depression

Australian Medicines Handbook section 18.1.4

Venlafaxine is a serotonin reuptake inhibitor which, at higher doses, also inhibits reuptake of noradrenaline. It is metabolised in the liver to desvenlafaxine which also has antidepressant actions. The decision to market the active metabolite might be related to the expiry of the patent on the controlled release formulation of venlafaxine.

Desvenlafaxine is well absorbed and only needs to be taken once a day. Although it is mainly metabolised by conjugation, desvenlafaxine is partly metabolised by cytochrome P450 3A4. Inhibitors of this enzyme, such as ketoconazole, may increase plasma concentrations of desvenlafaxine. The half-life of desvenlafaxine is 11 hours, but this may be increased by hepatic impairment. As almost half the dose is excreted unchanged in the urine, less frequent dosing is recommended for people with renal impairment.

Desvenlafaxine was compared to placebo in 234 patients with major depressive disorder. The mean score on the Hamilton Rating Scale for Depression was 23.7. The 120 patients randomised to use desvenlafaxine took 100 mg for two weeks then increased to 200 mg. After eight weeks the mean depression score had fallen to 14.1 with desvenlafaxine and 15.1 with placebo. This difference was not significant.[1]

A larger randomised trial evaluated the efficacy of daily desvenlafaxine in 114 patients who took 100 mg, 116 who took 200 mg, 113 who took 400 mg and in 118 who took a placebo. At the start of the study the mean score on the Hamilton Rating Scale for Depression was approximately 23. After eight weeks the mean reduction in the score was 10.6 with 100 mg, 9.6 with 200 mg, 10.7 with 400 mg and 7.7 with placebo. Only the reductions in the 100 mg and 400 mg groups were significantly better than the placebo response.[2]

Another eight-week study compared desvenlafaxine 200 mg and 400 mg to placebo. The scores on the Hamilton Rating Scale were reduced by 12.6 with 200 mg, 12.1 with 400 mg and by 9.3 with placebo.[3]

In the clinical trials the most common adverse effects of desvenlafaxine were nausea, dry mouth, somnolence, anorexia, constipation and nervousness.[1,2] Other adverse effects include vomiting, dizziness, blurred vision, sexual dysfunction, hypertension, increased cholesterol and triglycerides and altered liver function. Approximately 12% of patients who took desvenlafaxine withdrew from trials because of adverse events. Ideally, the dose should be tapered off as stopping the drug abruptly can cause discontinuation reactions.

Venlafaxine is metabolised to desvenlafaxine by cytochrome P450 2D6. Giving the metabolite as a drug bypasses this step so there could be less potential for drug interactions, but there is little evidence that desvenlafaxine has any advantage over venlafaxine. The precautions for prescribing the two drugs are similar. Overseas, the manufacturer applied to have desvenlafaxine approved for the treatment of menopausal hot flushes, but the US Food and Drug Administration has asked for more data and in Europe the application has been withdrawn.

The recommended dose in depression is 50 mg daily, but until recently there was little published information about this dose. Two trials have compared desvenlafaxine 50 mg and 100 mg to placebo. After eight weeks, both doses had reduced the scores on the Hamilton Rating Scale, but only the 50 mg dose was significantly better than placebo in both trials.[4,5] It appears that higher doses may have more adverse effects, but no additional benefit. For patients who are being satisfactorily managed with venlafaxine there seems little reason to change to desvenlafaxine.

T T manufacturer provided additional useful information

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Methylnaltrexone bromide

Relistor (Wyeth)

vials containing 12 mg/0.6 mL solution

Approved indication: opioid-induced constipation

Australian Medicines Handbook section 12.4.4

Constipation is one of the common adverse effects of opioid analgesics. This constipation is caused by several mechanisms such as altered smooth muscle tone in the gut.

Methylnaltrexone is related to the opioid antagonist naltrexone. Whereas naltrexone is particularly used to block the effects of opioids on the central nervous system, methylnaltrexone is more selective for peripheral opioid receptors. This is because adding a methyl group reduces lipid solubility which limits the molecule's ability to cross the blood-brain barrier. Blocking opioid receptors in the gut should relieve constipation without counteracting the analgesic effects of opioids.

While naltrexone is taken by mouth, methylnaltrexone has to be given by subcutaneous injection. It has a half-life of approximately eight hours and most of the dose is excreted unchanged, mainly in the urine. The dose is adjusted according to the patient's weight and is usually given on alternate days as needed.

A dose-ranging study was carried out in 33 patients receiving opioids for palliative care. For patients receiving a minimum dose of at least 5 mg the median time until a bowel movement was 1.26 hours. Almost half of these patients responded within four hours. Higher doses did not improve the response.[1]

A double-blind placebo-controlled trial was carried out in 133 terminally ill patients taking opioids and laxatives. They were given injections every other day for two weeks. A bowel motion occurred within four hours of the first injection in 48% of the methylnaltrexone group and in 15% of the placebo group. The median time between the injection and a bowel movement was 6.3 hours with methylnaltrexone, but more than 48 hours with placebo. After two weeks the response rate was 38% with methylnaltrexone and 8% with placebo. Pain scores were largely unchanged during the study.[2]

Patients given methylnaltrexone are more likely than those given placebo to complain of nausea, dizziness, flatulence, abdominal pain and increased temperature.[2] Diarrhoea can occur and if it is persistent, treatment should be discontinued. The drug should not be used if the patient is suspected of having an obstruction of the bowel.

The longer-term efficacy of methylnaltrexone is uncertain because the patients in the trials had a limited life expectancy. At present methylnaltrexone is reserved for palliative care patients with opioid-induced constipation whose response to laxatives has been insufficient.

T T T manufacturer provided clinical evaluation

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Rivaroxaban

Xarelto (Bayer Schering)

10 mg film-coated tablets

Approved indication: prevention of postoperative venous thrombosis

Australian Medicines Handbook section 7.1.3

The search for alternatives to heparin and warfarin has looked at different sections of the coagulation cascade. One approach is to inhibit activated factor X (Xa) which is responsible for the conversion of prothrombin to thrombin. Fondaparinux is an indirect inhibitor of factor Xa, but has to be given by injection. Rivaroxaban offers an oral alternative and has a more direct action.

Rivaroxaban is well absorbed from the gut and maximum inhibition of factor Xa occurs three hours after a dose. The effect lasts 8–12 hours, but factor Xa activity does not return to normal within 24 hours so once-daily dosing is possible. Rivaroxaban is eliminated in the urine and by metabolism. It is contraindicated in patients with significant renal or hepatic disease. As the hepatic metabolism involves cytochrome P450 3A4 there is a potential for interactions with drugs such as rifampicin and the azole antifungals. There are also theoretical interactions with inhibitors of the P-glycoprotein transporter, such as verapamil and diltiazem.

Anticoagulation after orthopaedic surgery on the lower limb can reduce the incidence of deep vein thrombosis. A dose-ranging study of rivaroxaban was therefore carried out in 873 patients having total hip replacements. These patients were randomised to one of five doses of rivaroxaban or a daily injection of enoxaparin. After 5–9 days of treatment the patients had venography. Deep vein thrombosis was less frequent in the patients taking rivaroxaban. There was no significant relationship between dose and efficacy, but the risk of major bleeding increased with dose.[1] A dose of 10 mg rivaroxaban was then selected for the Phase III trials called the RECORD studies.

RECORD1 randomised 2275 patients to daily injections of 40 mg enoxaparin and 2266 to take rivaroxaban after total hip replacement. Efficacy was assessed by venography after 35 days of prophylaxis. The primary outcome measure was a composite of death, pulmonary embolism and deep vein thrombosis. This outcome occurred in 3.7% of the enoxaparin group and 1.1% of the rivaroxaban group. There were four deaths in each group so the difference between the groups was accounted for by a significantly lower incidence of deep vein thrombosis with rivaroxaban.[2]

RECORD2 also studied patients having a total hip replacement and had the same primary efficacy outcome as RECORD1. A total of 2509 patients were randomised to daily injections of 40 mg enoxaparin for 10–14 days or rivaroxaban for 31–39 days. The enoxaparin group took placebo tablets and the rivaroxaban group had injections of placebo. After 32–40 days the patients had venography. The primary outcome occurred in 9.3% of the enoxaparin group and 2% of the rivaroxaban group. There were significantly fewer thromboses with rivaroxaban.[3]

RECORD3 had a similar primary efficacy outcome to the other trials, but enrolled patients having total knee replacements. A group of 1277 was randomised to receive 40 mg enoxaparin daily while a group of 1254 took rivaroxaban for 10–14 days. Venography after treatment found deep vein thrombosis in 18.2% of the enoxaparin group and 9.6% of the rivaroxaban group. The primary outcome occurred in 18.9% of the enoxaparin group and 9.6% of the rivaroxaban group.[4]

RECORD4 also studied patients who had knee replacement surgery, but compared rivaroxaban with an American regimen of enoxaparin (30 mg twice daily). The 3148 patients were treated for 10–14 days and had venography after 40 days. The primary outcome occurred in 10.1% of the enoxaparin group and 6.9% of the rivaroxaban group.

Although rivaroxaban prevents more thromboses than enoxaparin, the frequency of bleeding is slightly higher. In RECORD1 major bleeding occurred in 0.3% of the rivaroxaban group and 0.1% of the enoxaparin group.[2] In RECORD3 the corresponding figures were 0.6% and 0.5%.[4] Less serious, but clinically relevant, bleeding is also more frequent with rivaroxaban. The incidence of other adverse effects is similar for rivaroxaban and enoxaparin. Special precautions are needed if the patient has had spinal or epidural anaesthesia. Although rivaroxaban can increase the concentrations of liver enzymes it has not yet shown the toxicity which was associated with ximelagatran, another oral anticoagulant. More safety data will emerge from longer-term study of the drug in conditions such as atrial fibrillation. When used for short-term prevention of thrombosis, routine monitoring of the anticoagulant effect is not required.

If overdose occurs there is no specific antidote to rivaroxaban.

The currently available data suggest that rivaroxaban will be as effective as low molecular weight heparin for prophylaxis after surgery to the lower limb. Patients will probably prefer a daily tablet to a daily injection.

T manufacturer provided some information

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Triptorelin embonate

Diphereline (Ipsen)

6 mL vials containing 3.75 mg or 11.25 mg as powder for reconstitution

Approved indication: prostate cancer

Australian Medicines Handbook section 14.3.3

Locally advanced or metastatic prostate cancer can be managed by androgen ablation. This can be achieved by orchidectomy or hormonal treatment. Several agonists of luteinising hormone releasing hormone, such as goserelin and leuprorelin, are approved for this indication. Like other agonists, triptorelin initially causes a surge in luteinising hormone concentrations, but continued use reduces pituitary secretion. This leads to reduced androgen production with testosterone concentrations falling to levels similar to those seen after orchidectomy. Patients can be given a monthly intramuscular injection (3.75 mg) or an injection of the long-acting formulation (11.25 mg) every three months. As the molecule is a synthetic peptide it is probably degraded like a protein. Clearance is reduced by hepatic or renal impairment.

A South African trial randomised 172 men with advanced prostate cancer to have monthly injections and 174 to receive the long-acting formulation. After 29 days 93% of the patients on the monthly regimen and 98% of those on the three-monthly regimen had reached the target testosterone concentration. Both regimens maintained these concentrations in most patients during the 36 weeks of the study.

Another South African trial randomised 140 men to receive monthly triptorelin and 144 to receive monthly leuprorelin. After 29 days the proportion of men with target testosterone concentrations was significantly higher with leuprorelin (99% vs 91%). By 57 days there was no significant difference.[1]

The hormonal surge at the start of treatment may exacerbate symptoms, such as bone pain and bladder outflow obstruction. As treatment continues patients may complain of decreased libido, impotence, breast pain and hot flushes. Other adverse events include skeletal pain, hypertension, oedema, weight gain and pain at the injection site.

Although triptorelin has been available overseas for a few years there is little published information about its impact on survival. Although survival was not the primary end point of the comparative study, the nine-month survival rate was 97% with monthly triptorelin and 91% with leuprorelin.[1]

☒ manufacturer declined to supply data

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Valsartan

Diovan (Novartis)

80 mg and 160 mg film-coated tablets

Approved indications: hypertension, heart failure

Australian Medicines Handbook section 6.3.5

Valsartan/hydrochlorothiazide

Co-Diovan (Novartis)

80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg film-coated tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.3.5

Amlodipine/valsartan

Exforge (Novartis)

5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg film-coated tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.3.5

Valsartan

Valsartan is an angiotensin II antagonist which was launched overseas more than 10 years ago, but was not marketed in Australia. Like other members of the class, such as candesartan and losartan, valsartan lowers blood pressure by acting at the angiotensin type I receptor.

The antihypertensive effect of valsartan reaches a maximum after four weeks. Although raising the dose can increase the antihypertensive effect, doubling the dose from 160 mg to 320 mg may only reduce blood pressure by an extra 1–2 mmHg, while increasing adverse effects such as dizziness.[1]

Patients take the tablets once a day for hypertension and twice a day for heart failure. Most of the dose is excreted unchanged in bile, but it is recommended that the maximum dose should be limited in patients with severe renal impairment as well as in those with mild to moderate hepatic impairment. It is contraindicated in pregnancy.

A large trial has compared valsartan with amlodipine in more than 15 000 hypertensive patients. After a mean follow-up of 4.2 years the reduction in mean blood pressure was greater in patients taking amlodipine than in those taking valsartan. Systolic pressure fell by 17 mmHg with amlodipine and by 15 mmHg with valsartan, while the diastolic pressures fell by 10 mmHg and 8 mmHg. Although the composite end point of cardiovascular morbidity and mortality was not significantly different, there were more myocardial infarctions in the patients taking valsartan. The incidence of infarction per 1000 patient years was 11.4 with valsartan and 9.6 with amlodipine.[2]

Valsartan has been studied in patients with acute myocardial infarction. They were enrolled if they had signs of heart failure or left ventricular systolic dysfunction. More than 14 000 patients were randomised to receive valsartan, captopril or both drugs. After a median follow-up of 24.7 months, 19–20% of the patients in each group had died. Valsartan was not inferior to captopril, but their combination had no advantage and resulted in more patients stopping treatment because of adverse effects.[3]

Valsartan has also been used to treat chronic heart failure. In a controlled trial valsartan, or a placebo, was added to the treatment of 5010 patients with heart failure (New York Heart Association class II, III or IV). After a mean follow-up of 23 months, 19–20% of the patients in each group had died, however a combined end point of mortality and morbidity showed an advantage for valsartan. This was mainly because fewer patients, than in the placebo group, were admitted to hospital because of worsening heart failure (13.8% vs 18.2%). Valsartan should not be used in patients who are already taking an ACE inhibitor and a beta blocker. In the trial, adding valsartan to this combination significantly increased mortality.[4]

Valsartan with hydrochlorothiazide

In the comparison with amlodipine, more of the patients taking valsartan needed to take additional drugs, such as hydrochlorothiazide, to control their blood pressure.[2] These patients can now be considered for management with a combination tablet containing valsartan and hydrochlorothiazide.

There is an interaction between the drugs. Hydrochlorothiazide reduces the concentrations of valsartan and valsartan reduces the availability of hydrochlorothiazide. These changes do not negate the antihypertensive effect.

The combination of valsartan and hydrochlorothiazide was compared with valsartan in a placebo-controlled trial involving 871 patients with essential hypertension. These patients were randomised to one of nine groups using different doses of the combination, or monotherapy. After eight weeks all the active treatments had reduced the mean sitting blood pressure significantly more than placebo. Any combination of valsartan and hydrochlorothiazide reduced blood pressure more than either drug alone. For example, valsartan 80 mg with 12.5 mg of hydrochlorothiazide will reduce the diastolic pressure by 3.2 mmHg more than 80 mg valsartan and by 4.7 mmHg more than 12.5 mg hydrochlorothiazide.[5]

Another trial compared two combinations of valsartan and hydrochlorothiazide with valsartan alone in 774 patients with systolic hypertension. After eight weeks the mean sitting systolic blood pressure had been reduced by 20.7 mmHg with valsartan 160 mg. In combination with hydrochlorothiazide 12.5 mg the reduction was 27.9 mmHg and with hydrochlorothiazide 25 mg it was 28.3 mmHg.[6]

The combination of valsartan and hydrochlorothiazide has also been compared with amlodipine. In addition to hypertension, the 1088 patients in this study all had at least one other cardiovascular risk factor. After 24 weeks amlodipine 10 mg had reduced the mean systolic sitting blood pressure by 27.6 mmHg. Valsartan reduced the pressure by 27.1 mmHg when combined with hydrochlorothiazide 12.5 mg and by 29.7 mmHg with hydrochlorothiazide 25 mg.[7]

The main adverse effects of the combinations are dizziness, headache and fatigue.[5] Approximately 4% of patients will have a greater than 20% decrease in serum potassium.

Amlodipine with valsartan

Valsartan has also been combined with a calcium channel blocker to treat hypertension. The combination of amlodipine and valsartan is taken once daily. The bioavailability of the tablet is equivalent to that of its components when they are given separately. There is no significant interaction between the drugs, so their pharmacokinetic parameters are expected to be the same when they are given in a combined formulation.

Two placebo-controlled studies involving more than 3000 patients have compared the antihypertensive effects of amlodipine and valsartan alone with different strengths of the combination. Over eight weeks, most of the combined formulations produced significantly larger reductions in blood pressure than either drug alone or placebo.[8]

Another study compared the combined tablets (amlodipine 5 mg or 10 mg with valsartan 160 mg) with a combination of lisinopril and hydrochlorothiazide in 130 patients who had diastolic blood pressures of 110–119 mmHg. After six weeks both combinations had controlled the diastolic blood pressure in 77–80% of patients. The mean reduction in diastolic pressure with amlodipine and valsartan was 29 mmHg and with lisinopril and hydrochlorothiazide it was 28 mmHg.[9]

Combination products expose patients to the adverse effects of both components, but in some cases one drug may ameliorate the effects of the other. Peripheral oedema occurs in approximately 5% of those taking amlodipine and valsartan. This is significantly less than with amlodipine alone (9%), but more than with valsartan alone (2%).[8] Less frequent reactions are headache and dizziness.

Most patients will need more than one drug to control their blood pressure, but the treatment of hypertension should not begin with a combination product. Ideally, the doses of the individual drugs should be titrated to an optimum dose. If these doses correspond to those of a combination product, the patient can be switched to the combination. The problem with fixed dose combinations is that the ability to titrate the dose is limited.[10]

T manufacturer provided only the product information

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

* 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).

Answers to self-test questions

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

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