

# New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been 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.

## Carbetocin

Duratocin (Ferring)

ampoules containing 100 microgram/mL

Approved indication: prevention of uterine atony after Caesarian section

Australian Medicines Handbook section 17.7.1

Oxytocin is a hormone released from the posterior pituitary. As it stimulates rhythmic contractions of uterine smooth muscle, synthetic preparations can be used to induce or augment labour. Oxytocin can also be used to prevent postpartum haemorrhage.

Carbetocin is a synthetic analogue of oxytocin, with a longer half-life (41 minutes after intravenous injection vs 1–5 minutes). It stimulates a prolonged uterine response lasting about an hour.

The approved indications reflect the largest published trial of carbetocin. This involved 694 women who were having elective Caesarian sections under regional anaesthesia. The women were randomised to receive, after delivery, a bolus dose of oxytocin followed by an infusion, or a bolus dose of carbetocin followed by an infusion of placebo. In the oxytocin group, 10% of the women needed additional treatment to maintain the uterine contraction in the 48 hours after delivery. Only 6.3% of the women given carbetocin needed additional treatment.<sup>1</sup>

The adverse effects of carbetocin resemble those of oxytocin. They include abdominal pain, nausea, flushing and headache. Nearly half the patients may complain of itching.

While a single dose of carbetocin may be preferable to an infusion of oxytocin, after Caesarian section, it may not reduce blood loss more than oxytocin. In the main trial, the fall in postoperative haemoglobin was similar in both groups. Two women in each group had a postpartum haemorrhage.<sup>1</sup>

Carbetocin has not been studied after vaginal delivery or in women with a high risk of postpartum haemorrhage after Caesarian section. More research, including patient safety and economic evaluations, will therefore be needed before it can replace oxytocin as the first drug to use in the active management of the third stage of labour.

 manufacturer provided all requested data

## Reference

1. Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR, Luther ER, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol* 1999;180:670-6.

## Fulvestrant

Faslodex (AstraZeneca)

pre-filled syringes containing 250 mg/5 mL

Approved indication: advanced breast cancer

Australian Medicines Handbook section 14.4.2

Women with breast cancer that is hormone receptor positive are often given an anti-oestrogen, such as tamoxifen, as part of their treatment. Despite this treatment the cancer can still advance and metastasise. When this occurs the woman may be treated with an aromatase inhibitor such as anastrozole to further reduce the circulating oestrogen concentrations.

Fulvestrant offers another option for postmenopausal women with hormone receptor positive, locally advanced or metastatic breast cancer whose disease has progressed despite taking tamoxifen. It competitively binds to oestrogen receptors and leads to their down-regulation. Unlike tamoxifen, fulvestrant has no agonist activity at the oestrogen receptor.

Fulvestrant is formulated as an oily solution. There is a slow absorption after intramuscular injection so the peak plasma concentration is not reached for a week. Absorption continues for over a month and a steady state is reached after six injections at one-month intervals. The half-life is approximately 50 days. As fulvestrant is a steroid molecule it is mainly eliminated by metabolism. Less than 1% of the dose is excreted in the urine.

A double-blind trial compared fulvestrant and tamoxifen in 587 postmenopausal women with locally advanced or metastatic breast cancer. Their cancers were hormone receptor positive (or of unknown status) and they had not been recently treated with hormonal therapy. Approximately 33% of the women responded to treatment with a median time to progression of the cancer of 6.8 months with fulvestrant and 8.3 months with tamoxifen. After 31 months of follow-up, 48% of the fulvestrant group were dead compared to 43% of the tamoxifen group. Although the overall results favoured tamoxifen there was less difference in outcomes in women with hormone-receptor positive tumours.<sup>1</sup>

Two studies have compared monthly injections of fulvestrant with daily oral anastrozole in women with breast cancer that had progressed despite hormonal therapy. One of these studies was an open label trial which included some Australians among the 451 participants. After a median follow-up of 14.4 months the cancer had progressed in 82.4% of the women taking fulvestrant and in 83.4% of those taking anastrozole.<sup>2</sup> The other

study was a double-blind American trial involving 400 women. After a median follow-up of 16.8 months the cancer had progressed in 83.5% of the women taking fulvestrant and in 86.1% of those taking anastrozole.<sup>3</sup>

When the results of the two trials<sup>2,3</sup> were combined the median time to progression was calculated to be 5.5 months with fulvestrant and 4.1 months with anastrozole. After a median follow-up of 27 months 74.5% of the fulvestrant group and 76.1% of the anastrozole group were dead. There was no significant difference in the median overall survival (27–28 months).<sup>4</sup>

The frequency of adverse reactions to fulvestrant and anastrozole is similar<sup>2,3</sup> and neither drug has a greater effect than the other on the patient's quality of life. Commonly reported adverse events with fulvestrant include hot flushes, injection-site reactions, gastrointestinal upsets, bone pain and rashes. Thromboembolism has been reported, but as the risk of thrombosis may be increased in patients with breast cancer the association with fulvestrant is uncertain. The effect of fulvestrant on bone is unknown. It is also unknown if fulvestrant will be of benefit to women with an advanced cancer which has previously been treated with tamoxifen and has not responded to an aromatase inhibitor.

 manufacturer declined to supply data

## References \* †

1. Howell A, Robertson JF, Abram P, Lichinitser MR, Elledge R, Bajetta E, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* 2004;22:1605-13.
2. Howell A, Robertson JF, Albano JQ, Aschermannova A, Mauriac L, Kleeberg UR, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002;20:3396-403.
3. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol* 2002;20:3386-95.
4. Howell A, Pippen J, Elledge RM, Mauriac L, Vergote I, Jones SE, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma. A prospectively planned combined survival analysis of two multicenter trials. *Cancer* 2005;104:236-9.

## Natalizumab

Tysabri (Biogen-Idec)

glass vials containing 300 mg antibody in 15 mL liquid

Approved indication: monotherapy for relapsing-remitting multiple sclerosis

Australian Medicines Handbook section 14.1.4

Multiple sclerosis is characterised by the development of inflammatory lesions in the brain and spinal cord resulting in progressive disability for the patient. This process is mediated by immune cells that cross into the central nervous system. In most patients, the disease initially follows a relapsing-remitting course but eventually develops into a secondary progressive phase.

In Australia, there are currently two treatments for this disease, interferon beta and glatiramer, which act by modulating the immune system. Both of these drugs have been shown to reduce relapse rates by approximately 30% and retard disease progression by 12–18 months.<sup>1</sup>

Natalizumab, a humanised mouse monoclonal antibody, acts by binding to integrins present on the surface of leucocytes. This interaction stops the leucocytes from migrating into the central nervous system. Natalizumab may also suppress ongoing inflammation by preventing leucocytes from binding to ligands within the extracellular matrix.

Following the repeat intravenous administration of a 300 mg dose of natalizumab every four weeks, the serum concentration reaches a steady state after 24 weeks. The mean half-life of the drug is 11 days but clearance increases with body weight. After discontinuation, natalizumab stays in the blood for about 12 weeks, therefore a washout period may be appropriate before starting other treatments.

There have been three phase II trials and one phase III trial investigating natalizumab as a monotherapy for multiple sclerosis. In a placebo-controlled phase II trial, natalizumab (3 mg or 6 mg/kg) was given intravenously every four weeks for six months to patients with relapsing-remitting disease or secondary progressive multiple sclerosis. In the placebo group, 15 of 71 (21.1%) patients had at least one relapse compared with only 3 of 68 (4.4%) patients given natalizumab 3 mg/kg and 8 of 74 (10.8%) patients given natalizumab 6 mg/kg.<sup>2</sup>

Two other phase II trials also assessed natalizumab in patients with relapsing-remitting disease or secondary progressive multiple sclerosis. In the larger trial of 180 patients, a single dose of natalizumab (1 or 3 mg/kg) did not significantly improve the clinical course of acute relapses. Although natalizumab reduced the gadolinium-enhancing lesion volume in patients (observed by MRI) at 1 and 3 weeks after the beginning of treatment, by 14 weeks there were no differences in lesion volume between the treatment and placebo groups.<sup>3</sup>

In the other phase II trial of 72 patients, the number of new gadolinium-enhancing lesions was less in the treatment group

(two doses of natalizumab 3 mg/kg four weeks apart) compared to the placebo group over the first 12 weeks. However, in the second 12-week period there were no significant differences in the number of new lesions between the two groups.<sup>4</sup>

A phase III trial enrolled only patients with relapsing-remitting disease who had had a documented relapse in the previous 12 months. They received either a 300 mg dose of natalizumab or placebo every four weeks for up to 116 weeks. Of the 627 patients randomised to receive natalizumab, 72% remained relapse-free after two years compared with 46% of 315 patients randomised to the placebo group. Similarly after an MRI evaluation, no new or enlarging hyper-intense lesions were detected in 57% of patients in the natalizumab group compared with 15% of patients in the placebo group.<sup>5</sup>

During the phase III trial, 6% of natalizumab patients and 4% of placebo patients discontinued the study because of adverse effects. Infusion reactions occurred in 148 patients in the natalizumab group compared with 55 patients in the control group. Hypersensitivity reactions, which included urticaria, allergic dermatitis and anaphylaxis, were reported by 25 patients receiving natalizumab. There were five cases of cancer reported in the treatment group compared to one in the placebo group. Two deaths occurred during the trial. Both were in the natalizumab group; one was from malignant melanoma and the other was from alcohol intoxication.<sup>5</sup>

Persistent antibodies to natalizumab developed in 37 patients who also had an increase in infusion-related adverse events and loss of efficacy of the study drug.<sup>5</sup> It is known that the presence of such antibodies increases the clearance of natalizumab three-fold.

In 2005 natalizumab was voluntarily withdrawn in the USA following reports of progressive multifocal leukoencephalopathy, a serious viral infection of the brain, in approximately 1 in 1000 patients taking the drug. After confirming that there were no additional cases of the infection, natalizumab was re-released in the USA through a restricted prescribing program. The drug also comes with a warning to doctors and patients that it increases the risk of progressive multifocal leukoencephalopathy.

Natalizumab is contraindicated for patients who have an increased risk of opportunistic infections. It should not be given in combination with other drugs that modulate the immune system.

The safety and efficacy of natalizumab beyond two years is unknown. During treatment there is a possibility that patients will develop antibodies to this drug that may reduce its efficacy and cause a hypersensitivity reaction.

Natalizumab should only be given by a neurologist who has timely access to MRI facilities. Patients should be evaluated three and six months after the first infusion and then every six months. If there is no sign of clinical benefit after six months, consider discontinuing treatment.

**T** manufacturer provided only the product information

## References \* †

1. Taylor I, Macdonell R, Coleman J. Treatment of multiple sclerosis with newer immune-modulating drugs. *Aust Prescr* 2002;25:32-5.
2. Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, et al; the International Natalizumab Multiple Sclerosis Trial group. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2003;348:15-23.
3. O'Connor PW, Goodman A, Willmer-Hulme AJ, Libonati MA, Metz L, Murray RS, et al; the Natalizumab Multiple Sclerosis Trial group. Randomized multicenter trial of natalizumab in acute MS relapses. Clinical and MRI effects. *Neurology* 2004;62:2038-43.
4. Tubridy N, Behan PO, Capildeo R, Chaudhuri A, Forbes R, Hawkins CP, et al; the UK Antegren Study group. The effect of anti-alpha4 integrin antibody on brain lesion activity in MS. The UK Antegren Study Group. *Neurology* 1999;53:466-72.
5. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al; the AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899-910.

## Pentastarch

Voluven (Pharmatel Fresenius Kabi)

6% solution for intravenous infusion

Approved indication: hypovolaemia

The optimum solution for expanding plasma volume is uncertain. There is debate about whether patients given colloid solutions, such as albumin, have worse outcomes than patients given crystalloid solutions.<sup>1</sup> To address some of the concerns synthetic colloids have been developed.

Pentastarch is derived from amylopectin. To slow down its metabolism by amylase, hydroxyethyl groups are added to the molecule. After this formulation is infused the expansion in intravascular volume lasts for 4–6 hours.

This formulation has been compared with other colloids in relatively small numbers of patients. Some of these comparisons have been with similar products containing a different ratio of hydroxyethyl groups.

In cardiac surgery there was no difference in efficacy between the new formulation and a similar product with a higher molecular weight.<sup>2</sup> A study in orthopaedic surgery had a similar result and found that the new formulation may have less effect on some coagulation factors.<sup>3</sup>

Patients may develop hypersensitivity reactions, including anaphylaxis, to pentastarch. Itching is common. There may be confusion about pancreatitis as amylase concentrations rise in patients given pentastarch.

While pentastarch is effective, many factors including cost and physicians' opinions will determine whether it is used in preference to other volume expanders.<sup>1</sup>

**T** manufacturer provided only the product information

## References

1. Miletin MS, Stewart TE, Norton PG. Influences on physicians' choices of intravenous colloids. *Intensive Care Med* 2002;28:917-24.
2. Gallandat Huet RC, Siemons AW, Baus D, van Rooyen-Butijn WT, Haagenaars JA, van Oeveren W, et al. A novel hydroxyethyl starch (Voluven) for effective perioperative plasma volume substitution in cardiac surgery. *Can J Anesth* 2000;47:1207-15.
3. Langeron O, Doelberg M, Ang E-T, Bonnet F, Capdevila X, Coriat P. Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. *Anesth Analg* 2001;92:855-62.

## Perflutren

Definity (Bristol-Myers Squibb)

vials containing 6.52 mg/mL

Approved indications: echocardiography, ultrasound of liver and kidney

Ultrasound studies, such as echocardiography, are not always clear. To improve image quality it may be necessary to use a contrast medium.

Perflutren is a gas so it will produce echoes which are distinct from those of the surrounding tissues. To transport this inert gas to the heart, it has to be enveloped in a microsphere. A vial containing perflutren and liquid lipid is shaken by a machine for 45 seconds. This creates a suspension containing perflutren within lipid microspheres. The activated substance is then slowly injected intravenously or given as an infusion, depending on the investigation. Its half-life is less than two minutes with the gas being eliminated through the lungs.

Perflutren has been compared with saline in 211 patients, who had previously had a suboptimal echocardiography, in a double-blind trial. Depending on the dose, perflutren enhanced the imaging of the left ventricle in 87–91% of patients. There was no enhancement with saline.<sup>1</sup> In addition to opacifying the cardiac chambers, perflutren can be used in regional wall motion studies. After administration of perflutren the agreement with magnetic resonance imaging of wall motion increased, however it did not improve the accuracy of measurements of the ejection fraction. Although there have been fewer trials, perflutren has also been approved for use in characterising focal lesions in the liver and kidney.

Injecting patients with gas bubbles is not without risk, particularly in patients who may have a cardiac shunt or compromised pulmonary vessels. Patients with congestive heart failure also have a higher incidence of adverse effects. While headache is the most frequent adverse reaction, there have been serious hypersensitivity reactions and seizures. This has prompted a revision of the product information in the USA.

 manufacturer provided clinical evaluation

## Reference \* †

1. Kitzman DW, Goldman ME, Gillam LD, Cohen JL, Aurigemma GP, Gottdiener JS. Efficacy and safety of the novel ultrasound contrast agent perflutren (Definity) in patients with suboptimal baseline left ventricular echocardiographic images. *Am J Cardiol* 2000;86:669-74.

## Tipranavir

Aptivus (Boehringer Ingelheim)

250 mg capsules

Approved indication: HIV

Australian Medicines Handbook section 5.4.3

Protease inhibitors can be used as components in combination regimens for HIV infection (see 'New developments in antiretroviral therapy for HIV infection', *Aust Prescr* 2005;28:146–9). As the virus can develop resistance there is a need to find treatments which work when these regimens fail. There are already eight protease inhibitors available in Australia, so tipranavir is reserved for patients who have viral replication with HIV strains that are resistant to multiple protease inhibitors.

Although tipranavir inhibits HIV production in the same way as other protease inhibitors it is not a peptide. *In vitro* it retains antiviral activity against strains that have decreased susceptibility to protease inhibitors.

Tipranavir is poorly absorbed so several doses would be needed to reach effective concentrations. However, a twice-daily dose is possible if ritonavir is also taken. Ritonavir inhibits cytochrome P450 3A and the P-glycoprotein pump, significantly increasing the plasma concentrations of tipranavir. In the presence of ritonavir there is very little metabolism of tipranavir and most of the dose is excreted in the faeces. The elimination half-life is approximately six hours.

In a dose-response study 31 untreated patients were randomised to take different doses of tipranavir, with or without ritonavir, for 14 days. All three regimens reduced viral RNA concentrations, but the greatest effect was in the two regimens containing ritonavir.<sup>1</sup>

Two open-label studies have assessed regimens including tipranavir and ritonavir in patients who had previously been treated with at least two protease inhibitors. Although the studies were not complete, tipranavir was approved on the basis of the results of 24 weeks treatment. A total of 1177 patients were randomised to take tipranavir with ritonavir or another protease inhibitor with ritonavir, in addition to other antiviral drugs. At 24 weeks 34% of the tipranavir group and 15% of the comparator group had less than 400 viral copies/mL. While only 9% of the comparator group had less than 50 copies/mL, 24% of the tipranavir group had reached this concentration. There was an increase of 34 CD4 cells/mm<sup>3</sup> with tipranavir but only 4 cells/mm<sup>3</sup> with the comparator drugs.

Although more patients responded to tipranavir it also caused more people (8% vs 4%) to discontinue treatment because of adverse events. The most common adverse reactions are diarrhoea, nausea, vomiting, fever, fatigue and headache. Altered liver function and dyslipidaemia are more frequent than with other protease inhibitors. Tipranavir is contraindicated if there is impaired liver function so frequent monitoring is needed. Patients should not be given drugs, such as midazolam, which are cleared by cytochrome P450 3A. There are many other drugs which may interact with tipranavir, particularly as it will be used in combination with ritonavir.

Preliminary data suggest that tipranavir will have a role in treating patients with resistant HIV. To define this role genotypic testing is recommended. At present the data about which mutations may have increased resistance to tipranavir are unclear.

**T** manufacturer provided only the product information

## Reference \*†

1. McCallister S, Valdez H, Curry K, MacGregor T, Borin M, Freimuth W, et al. A 14-day dose-response study of the efficacy, safety, and pharmacokinetics of the nonpeptidic protease inhibitor tipranavir in treatment-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2004;35:376-82.

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](http://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](http://www.emea.europa.eu)).

## Answers to self-test questions

- |          |          |          |          |
|----------|----------|----------|----------|
| 1. False | 3. False | 5. False | 7. False |
| 2. False | 4. True  | 6. False | 8. True  |

## [www.australianprescriber.com](http://www.australianprescriber.com)

*Australian Prescriber* is available on the internet in full text, free of charge. Go to **New issue email alert** to be sent an email each time a new issue goes online.

## *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 all the available back issues

Name: .....

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

Address: .....  
.....  
.....

Profession: .....

(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist etc.)

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

Telephone: (02) 6241 6044 Fax: (02) 6241 5768

## 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](mailto:info@australianprescriber.com)

Website: [www.australianprescriber.com](http://www.australianprescriber.com)