

## Breaches of the Code (Table 1)

In the interests of transparency, the Code includes a requirement for regular publication of Code breaches in medical journals. This information includes the names of companies who have had complaints brought against them, a summary of the complaints and sanctions imposed.

In 1999–2000 44 complaints were received. (Six of these were subsequently withdrawn, one was referred elsewhere and three were returned to the complainant.) Of the 34 complaints evaluated by the Committee, 28 were found to be in breach of the Code. There was a variety of problems dealt with by the Committee (see box).

Two complaints were found not to be breaches of the Code, but prompted the APMA to consider modifications to the Code:

- a complaint about using a telemarketing campaign to advise prescribers of a change in the availability of Losec
- a complaint about sending letters to patients encouraging them to lobby their Members of Parliament to support the listing of Aricept on the Pharmaceutical Benefits Scheme.

## REFERENCES

1. Australian Pharmaceutical Manufacturers Association. Code of Conduct of the Australian Pharmaceutical Manufacturers Association. 13th ed. Sydney: Australian Pharmaceutical Manufacturers Association Inc.; 2000.
2. Roughead EE. The Australian Pharmaceutical Manufacturers Association Code of Conduct: guiding the promotion of prescription medicines. Aust Prescr 1999;22:78-80.

## Examples of Code breaches

### *Oxycontin*

Statements in the promotional material overstated the attributes of oxycontin and promised more than the product could reasonably be expected to deliver. One statement was probably misleading because it implied that oxycontin is first-line therapy (contrary to the approved indications). Statements used in an unqualified manner may have encouraged excess usage of oxycontin and were therefore inappropriate and misleading.

### *Kliovance*

Healthcare professionals were invited to participate in a project that was not clearly identified as market research. Offering payment for their participation in a Product Familiarisation Programme and giving them a three month free supply of Kliovance was not permitted under the Code.

## NOTE

The APMA Code of Conduct is available from:

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<http://www.apma.com.au>

# 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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

## Brinzolamide

Azopt (Alcon)

10 mg/mL in 5 mL dispensers

Approved indication: raised intraocular pressure

Australian Medicines Handbook Section 11.2.7

Conditions such as open-angle glaucoma cause increases in intraocular pressure which can result in blindness. The intraocular pressure can be reduced by drugs which decrease the production, or increase the outflow, of aqueous humour. Carbonic anhydrase inhibitors reduce the production of aqueous humour and can be given topically. Dorzolamide was the first topical member of the class to be approved in Australia.

Brinzolamide is structurally similar to dorzolamide. It has a high affinity for carbonic anhydrase-II, the predominant form of the enzyme in the eye. After brinzolamide is instilled into the eye, some drug is absorbed into the circulation. It is mainly distributed to the red blood cells. As the half-life of brinzolamide in whole blood is 111 days, it takes 6–9 months for the drug concentrations to reach a steady state. These concentrations are not great enough to interfere with the normal functions of carbonic anhydrase in the body.

During short-term clinical trials a twice-daily dose of brinzolamide 1% has reduced intraocular pressure by approximately 3–5 mmHg. In an 18-month study the mean reductions in intraocular pressure were 2.7–3.9 mmHg with brinzolamide and 4.7–5.6 mmHg with timolol 0.5% (a topical beta blocker).<sup>1</sup> Another study compared brinzolamide 1% with dorzolamide 2%, and timolol 0.5% for three months. All three drugs had similar effects on intraocular pressure and there were no significant differences in the efficacy of the two carbonic anhydrase inhibitors.<sup>2</sup> Adding brinzolamide to treatment with timolol can produce further reductions in intraocular pressure.

Most of the adverse effects of brinzolamide are related to the instillation of the drops. Patients may develop blurring of vision, and sore or painful eyes. They may also complain of a bitter taste.

Although brinzolamide has been used as monotherapy, the carbonic anhydrase inhibitors are second-line drugs. A three-times daily dose was used in some clinical trials, but 76% of patients will respond adequately to a twice-daily dose of brinzolamide.<sup>2</sup> This may give the drug an advantage over dorzolamide which is instilled three times a day. Another

advantage is that brinzolamide instillation causes significantly less discomfort.<sup>2</sup>

#### REFERENCES

1. Brinzolamide Long-Term Therapy Study Group. The long-term safety and efficacy of brinzolamide 1.0% (Azopt) in patients with primary open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2000;129:136-43.
2. Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 1998;126:400-8.

### Etonogestrel

Implanon (Organon)

68 mg implants

Approved indication: contraception

Australian Medicines Handbook Section 17.1.4

The approval of etonogestrel implants adds to the choice of progestogen-only methods of contraception. Etonogestrel is a metabolite of desogestrel which is used in some combined contraceptive pills.

The implant is 40 mm long and has a diameter of 2 mm. It is loaded inside a stainless steel applicator. After anaesthetising the area, the implant is inserted under the skin of the inner side of the upper arm. The inserting is done in the first five days of the menstrual cycle if the woman is not using the contraceptive pill. Women changing from a progestogen-only pill can have the implant at any stage of the cycle.

While etonogestrel does affect the cervical mucus, its main contraceptive effect is the inhibition of ovulation. Inhibitory concentrations of etonogestrel are reached within one day of insertion. One implant will release these concentrations of etonogestrel for at least two years. It should be removed after three years. The effect of etonogestrel quickly wears off after the implant is removed. This may be useful when managing adverse effects.

In clinical trials no pregnancies have occurred. The main problems have been the adverse effects associated with progestogens. The menstrual pattern is likely to change, some women will have irregular bleeding, others will have amenorrhoea. These changes often prompt women to ask for the implant to be removed. Other adverse effects include breast pain, acne and weight gain.

Prescribers who intend to offer etonogestrel as a contraceptive option should ensure they are instructed in how to insert and remove the implant.

### Infliximab

Remicade (Schering-Plough)

vials containing 100 mg as lyophilised powder

Approved indication: Crohn's disease

Australian Medicines Handbook Section 14.1.4

Crohn's disease causes chronic inflammation in the gastrointestinal tract. With time it tends to respond less well to treatment and many patients will develop complications such as a fistula. The cause of the disease is unknown, but an

immune mechanism may be involved. Patients with Crohn's disease produce increased amounts of tumour necrosis factor alpha (TNF-alpha). This factor may be responsible for inducing the mucosal inflammation.

Animal studies found that inflammation can be reduced by antibodies to TNF-alpha. Infliximab is a monoclonal antibody which neutralises TNF-alpha in humans. It was studied in a randomised controlled trial of 108 patients with moderate to severe Crohn's disease. Four weeks after a single infusion, 65% of the patients given infliximab had a clinical response compared with only 17% of the patients given a placebo. The disease went into remission in 33% of the infliximab group but only 4% of the placebo group.<sup>1</sup>

Another study investigated 94 patients with abdominal or perianal fistulas. These patients were given an infusion of infliximab or a placebo. This infusion was repeated two weeks and six weeks later. The number of draining fistulas decreased by half in 62% of the infliximab group compared with 26% of the placebo group. In 46% of the infliximab group the fistulas healed, while only 13% of the placebo group had an absence of any draining fistulas.<sup>2</sup>

Infliximab is a human form of a mouse monoclonal antibody produced using recombinant techniques. Approximately 16% of patients will have a reaction to its infusion. They may develop urticaria, fevers and chills. Some patients experience falls or rises in blood pressure so it is important that they are observed during and after the two hour infusion. Patients who develop antichimeric antibodies are more likely to have infusion reactions. These antibodies could also alter the pharmacokinetics of infliximab. The half-life of infliximab is normally about 10 days and it takes up to six months for serum concentrations to become undetectable.

Approximately 5% of patients withdrew from clinical trials of infliximab because of adverse events. Apart from infusion reactions adverse effects include headache, nausea, vomiting and abdominal pain. The patients given infliximab developed more infections than patients given a placebo. Although infliximab does not cause a generalised suppression of the immune system, caution is needed particularly if the patient has been taking immunosuppressive drugs for their Crohn's disease. It is unclear if infliximab increases the risks of developing lymphoproliferative disorders. Some patients will develop autoantibodies and cases of a lupus-like syndrome have been reported.

More information is needed on the long-term effectiveness of infliximab. In the short-term study the proportion of patients with a clinical response after 12 weeks had declined and the number of patients in remission was not significantly different from placebo.<sup>1</sup> If symptoms recur the treatment can be repeated within 14 weeks. Readministration after this period is currently not recommended because of the risk of delayed hypersensitivity reactions.

Recombinant products tend to be expensive. Infliximab is therefore reserved for patients who have not responded to conventional therapies for moderate to severe Crohn's disease.

## REFERENCES

1. Crohn's disease cA2 Study Group. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor  $\alpha$  for Crohn's disease. *N Engl J Med* 1997;337:1029-35.
2. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-405.

**Oseltamivir phosphate**

Tamiflu (Roche)

75 mg capsules

Approved indication: influenza

Australian Medicines Handbook Section 5.3.2

Oseltamivir is the second neuraminidase inhibitor to receive Australian approval for the treatment of influenza. Unlike its predecessor, zanamivir, oseltamivir is taken by mouth.

After absorption oseltamivir is converted to its active form, oseltamivir carboxylate. The plasma concentrations of this metabolite reach a peak within three hours and then decline with a half-life of 6–10 hours. Oseltamivir carboxylate is excreted in the urine, so the dose should be reduced if renal function is impaired.

In a clinical trial, twice-daily doses of 75 mg or 150 mg were compared with a placebo. The 629 adults involved in the trial had presented within 36 hours of developing a febrile respiratory illness. Laboratory testing confirmed the presence of influenza virus (mostly influenza A) in 374 cases. In these cases oseltamivir reduced the duration of illness by more than 30%.<sup>1</sup>

Patients given oseltamivir are more likely to experience gastrointestinal upsets than those given a placebo. In clinical trials 12% of patients suffered vomiting and a further 11% complained of nausea. There is potential for the influenza virus to develop resistance.

Although patients treated with oseltamivir recover significantly faster than those given a placebo, the difference is only about one day. Treating 1000 patients reduces illness by 254 hours. However, patients given 75 mg twice a day were able to resume their normal activities 2–3 days sooner than those given a placebo. Giving a higher dose does not make patients recover more quickly.<sup>1</sup> As few elderly or debilitated people were included in the clinical trials, the best strategy for those at risk is still immunisation to prevent influenza. Little information is available about the efficacy of oseltamivir in influenza B.

## REFERENCE

1. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *JAMA* 2000;283:1016-24.

**Rabeprazole**

Pariet (Janssen-Cilag)

10 mg and 20 mg enteric-coated tablets

Approved indications: peptic ulcer, gastro-oesophageal reflux disease

Australian Medicines Handbook Section 12.1.4

Rabeprazole is the fourth proton pump inhibitor to be approved in Australia. The other members of the class are omeprazole,

lansoprazole and pantoprazole. These drugs are potent inhibitors of acid secretion.<sup>1</sup>

The suppression of acid secretion begins within an hour of taking rabeprazole and lasts for up to 48 hours. This duration of action is much greater than the one hour half-life. The drug is metabolised by the cytochrome P450 system (CYP3A4 and CYP2C19) with most of the metabolites appearing in the urine.

Rabeprazole has been compared with omeprazole for each of its approved indications. Although many patients with duodenal ulcer will require treatment for *Helicobacter pylori*, the proton pump inhibitors can also be effective. After four weeks of treatment rabeprazole and omeprazole had healed more than 90% of the patients. Similar results were found after treating patients with gastric ulcers for six weeks, and patients with erosive or ulcerative gastro-oesophageal reflux disease for eight weeks. If patients with gastro-oesophageal reflux take rabeprazole or omeprazole for a year only about 5% will have a relapse.

Like other proton pump inhibitors rabeprazole is well tolerated. The commonest complaints in clinical trials included diarrhoea, headache and nausea. There have been reports of erythema and bullous skin reactions.

The product information states that rabeprazole does not have clinically significant interactions with other drugs metabolised by cytochrome P450. Rabeprazole does, however, interact with digoxin and ketoconazole.

Although rabeprazole may reduce the pain of peptic ulcer more than omeprazole, it has no clear advantage. The cost of rabeprazole may determine if it is widely prescribed.

## REFERENCE

1. Yeomans ND. Drugs that inhibit acid secretion. *Aust Prescr* 2000;23:57-9.

**Tenecteplase**

Metalyse (Boehringer Ingelheim)

vials containing 8000 IU and 10 000 IU

Approved indication: thrombolysis

Australian Medicines Handbook Section 7.3

For more than a decade, patients with acute myocardial infarctions have been treated with infusions of thrombolytic drugs such streptokinase. The aim of treatment is to restore the blood flow through the coronary artery related to the infarct. Research has aimed at developing drugs which restore more blood flow and do not require a prolonged infusion.

Alteplase is a genetically engineered plasminogen activator. (The activation of plasminogen produces plasmin which breaks down the fibrin in the thrombosis.) Tenecteplase has a similar structure to alteplase and is also produced by genetic engineering. The differences in structure give tenecteplase better fibrin specificity and a longer half-life than alteplase.

Tenecteplase can be given by a single bolus injection. This will improve the blood flow through the infarct-related artery in most patients within 90 minutes. The elimination is biphasic

with a terminal half-life of approximately two hours. Clearance is by hepatic metabolism.

A large study involving nearly 17 000 patients has compared a bolus of tenecteplase with a 90 minute infusion of alteplase. All the patients were meant to be treated within six hours of developing the symptoms of acute myocardial infarction. They were also given aspirin and heparin. After 30 days a similar proportion of each treatment group had died. The mortality rate for tenecteplase was 6.18% and it was 6.15% for alteplase.<sup>1</sup>

Fibrinolytic drugs increase the risk of stroke. In the comparative trial 1.78% of the patients given tenecteplase had a stroke compared with 1.66% of the alteplase group. While the frequency of intracranial bleeding was the same for both drugs, tenecteplase caused significantly fewer non-cerebral haemorrhages. Only 4.3% of the tenecteplase group needed a blood transfusion compared with 5.5% of the alteplase group.<sup>1</sup>

Despite the reduced need for transfusion, haemorrhage is still a common complication. More than 26% of the tenecteplase group had a bleeding complication. Tenecteplase is contraindicated in patients with an increased risk of bleeding. This includes patients with severe hypertension, peptic ulcers within the last three months, those who are taking warfarin and those who have had recent surgery or trauma, including cardiac resuscitation.

Although most patients in the clinical trial were treated soon after their infarction, tenecteplase has been approved for use up to 12 hours later. This matches the indication for alteplase. While tenecteplase seems to have a few advantages over alteplase, its relative cost-effectiveness will determine if it becomes the preferred treatment option.

#### REFERENCE

1. ASSENT-2 investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999;354:716-22.

### NEW DELIVERY SYSTEMS

#### Levonorgestrel

Mirena (Schering)

intrauterine device containing 52 mg levonorgestrel

Approved indications: contraception, menorrhagia, hormone replacement therapy

Australian Medicines Handbook Section 17.1.2

This product is a T-shaped intrauterine device with a cylinder of levonorgestrel around the long arm. The levonorgestrel is covered by a membrane which controls the release of the drug. At first the release rate is 20 microgram per day. The device contains enough levonorgestrel to last for five years.

The actions of levonorgestrel in the uterine cavity have a contraceptive effect (see 'Progestogen-only methods of contraception' *Aust Prescr* 1999;22:6-8). Contraceptive protection is immediate because the product also acts as an intrauterine contraceptive device. The contraception is highly

effective with a pregnancy rate of 0.16 per 100 women years, however 37% of these pregnancies are ectopic.

If there are no organic causes, the device can be used to treat menorrhagia. For some women it is preferable to hysterectomy.<sup>1</sup> The device's ability to prevent endometrial hyperplasia also enables it to be used to provide the progestogenic component in regimens of continuous hormone replacement therapy.

Some of the levonorgestrel is absorbed into the circulation and may inhibit ovulation. While there are other general effects such as acne, breast tenderness and weight changes, most adverse reactions affect the urogenital system. The menstrual pattern changes with spotting being a particular problem in the first few months after insertion. Increased bleeding or pain may be symptoms that the device is being expelled. The expulsion rate over five years is 2-6 per 100. Without the device in place, fertility soon returns. Conception occurs within a year in 80% of the women who have the device removed in order to become pregnant.

Pelvic infection may occur less frequently than with other intrauterine devices, but pelvic inflammatory disease is still a contraindication. The device should be removed if a pelvic infection does not rapidly respond to antibiotics.

While a levonorgestrel-releasing device may have some advantages it is not suitable for all women. It should not be the first choice for contraception in young nulliparous women. The device may also be unsuitable for postmenopausal women if atrophic changes have narrowed the cervical canal.

#### REFERENCE

1. Lahteenmaki P, Haukkamaa M, Puolakka J, Riikonen U, Sainio S, Suvisaari J, et al. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *Br Med J* 1998;316:1122-6.

### NEW FORMULATIONS

#### ***Clostridium botulinum* type A toxin-haemagglutinin complex**

Dysport (Ipsen)

500 IPSEN Units lyophilised powder

(Dysport is not therapeutically equivalent to the other botulinum toxin preparation currently available on the Australian market.)

#### **Flurbiprofen**

Strepfen (Boots Healthcare)

8.75 mg lozenges

#### **Oxycodone hydrochloride**

OxyNorm (Mundipharma)

5 mg capsules

### NEW STRENGTHS

#### **Cerivastatin sodium**

Lipobay (Bayer)

400 microgram tablets

**Oestradiol**

Climara 25 (Schering)  
 1.97 mg transdermal patches  
 Climara 75 (Schering)  
 5.69 mg transdermal patches

**NEW PROPRIETARY BRANDS**

**Enalapril maleate**

Alphapril (Alphapharm)  
 5 mg, 10 mg and 20 mg tablets

**Lisinopril**

Lisodur (Alphapharm)  
 5 mg, 10 mg and 20 mg tablets

**Mometasone furoate**

Allermax (Schering-Plough)  
 50 microgram per actuation aqueous nasal spray

**Oestradiol valerate/cyproterone acetate**

Climen 28 (Schering)  
 packs containing 16 oestradiol valerate 2 mg tablets and  
 12 oestradiol valerate 2mg/cyproterone acetate 1 mg tablets

**Salbutamol**

Epaq Inhaler (Arrow)  
 100 microgram per dose

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**Answers to self-test questions**

- 1. False
- 2. False
- 3. False
- 4. False