

Timely, independent information about new drugs

Atorvastatin (Lipitor) for the management of lipid disorders

Exempted from statin class PBS price reduction

01

Anastrozole (Arimidex) for the treatment of hormone-dependent early breast cancer in postmenopausal women

Expanded PBS listing December 2005

06

Buprenorphine transdermal patches (Norspan) for chronic severe pain

New product PBS listed December 2005

10

In Brief

High-strength fluticasone inhalers remain PBS listed — Pethidine to be deleted from doctor's bag supplies — Changes to narcotic analgesic prescribing — Benzodiazepines and NSAIDs on palliative care list — More information about PBAC decisions — New web extras

14

Welcome to the fourth printed issue of *NPS RADAR*.

NPS RADAR provides timely, independent, evidence-based information on new drugs, research and PBS listings. It is published three times a year in line with the *Schedule of Pharmaceutical Benefits*, for general practitioners, specialists, pharmacists and other health professionals.

A significant development slipped relatively unannounced onto the Department of Health and Ageing website on 28 October 2005. For the first time, the community had access to information providing insight into the decision-making process that determines which medicines are listed on the Pharmaceutical Benefits Scheme (PBS).

One of the consequences of the Free Trade Agreement between Australia and the United States was that greater openness was permitted to release the reasons for Pharmaceutical Benefits Advisory Committee (PBAC) decisions in the form of a 'public summary document' (PSD).

PSDs are generated after major submissions seeking listing on the PBS and are based on the minutes of the PBAC meeting. They outline the clinical and economic data that the Committee considered in arriving at their recommendation. A PSD will be produced both for positive recommendations to list a drug on the PBS as well as for negative recommendations. It is intended that the PSD will assist in understanding the context of a decision for people outside the PBAC process.

The first PSDs released pertain to decisions made in the July 2005 meeting of the PBAC and are available on the Department of Health and Ageing website (www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-outcomes-and-public-summary-documents). Examples include a recommendation to list strontium ranelate (Protos) as a new agent for treating osteoporotic fracture in postmenopausal women and a recommendation not to list insulin glargine (Lantus) for diabetes mellitus.

For prescribers and other health professionals, using a PSD and *NPS RADAR* review as companion pieces will provide a more complete picture about new drugs listed on the PBS. While the PSD provides context to the PBAC's decision within the framework of listing on the PBS, *NPS RADAR* advises on applying the listing to clinical practice by providing information on the place in therapy of the new drug relative to other therapies. Useful details about significant safety considerations and dosing issues, as well as pertinent points of discussion between health professionals and patients, make the role of *NPS RADAR* quite distinct from that of the PSDs.

In this issue of *NPS RADAR*:

- the review on atorvastatin (Lipitor) looks at the evidence comparing it with other statins and if there is any basis for preferring one statin over another (p.1)
- the PBS listing for anastrozole (Arimidex) was recently broadened to include treating all postmenopausal women with early or advanced hormone-dependent breast cancer; the *NPS RADAR* review (p.6) looks at the role of adjuvant therapy and compares anastrozole with tamoxifen
- buprenorphine is a partial opioid agonist that has been used for many years for opioid dependence and intra-operative analgesia. A newly formulated transdermal buprenorphine patch (Norspan) has been PBS listed for patients with non-cancer pain requiring a strong opioid. *NPS RADAR* considers what this new presentation adds to the opioid analgesic alternatives (p.10).

Timely, independent information about new drugs

National Prescribing Service Ltd

National Prescribing Service Limited (NPS) is a member-based organisation providing accurate, balanced, evidence-based information and services to health professionals and the community on Quality Use of Medicines (QUM). To achieve this we work in partnership with GPs, pharmacists, specialists, other health professionals, government, pharmaceutical industry, consumer organisations and the community. NPS is an independent non-profit organisation funded by the Australian Government Department of Health and Ageing.

Atorvastatin (Lipitor) for the management of lipid disorders

(a-TOR-va-stat-in)

Summary

- Atorvastatin is more potent at lowering plasma cholesterol levels compared with simvastatin and pravastatin.
- If existing treatment with simvastatin or pravastatin achieves target cholesterol levels, it is not necessary to switch to a more potent statin.
- High doses of atorvastatin (40 mg, 80 mg) achieve reductions in cholesterol that are not possible with the recommended doses of simvastatin.
- There are currently no head-to-head studies comparing the clinical outcomes of atorvastatin with equipotent doses of other statins.
- Choose the lowest effective dose of atorvastatin to achieve the current recommended target cholesterol level.
- All statins can cause myopathy or rhabdomyolysis, but this is rare.
- Elevated liver transaminase levels can occur with statins, particularly at high doses.

PBS listing

Atorvastatin is listed on the PBS as a restricted benefit for use in patients who meet the criteria set out in the General Statement for Lipid-Lowering Drugs Prescribed as Pharmaceutical Benefits (refer to the *Schedule of Pharmaceutical Benefits*). On 1 August 2005, new generic brands of simvastatin were listed on the PBS, resulting in a 12.5% price reduction across the statin class to brands of simvastatin, pravastatin and fluvastatin.¹ Atorvastatin was exempt from this price reduction and has maintained its price on the PBS.¹

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee accepted that atorvastatin is more effective than simvastatin in lowering cholesterol levels and that this justifies a price difference.¹ Economic analyses were based on percentage changes in lipid parameters derived from a meta-analysis of atorvastatin and its comparator, simvastatin. Head-to-head studies of the clinical outcomes of atorvastatin compared with simvastatin were not available, so the economic analysis was validated using the clinical outcomes from placebo-controlled studies.

Place in therapy

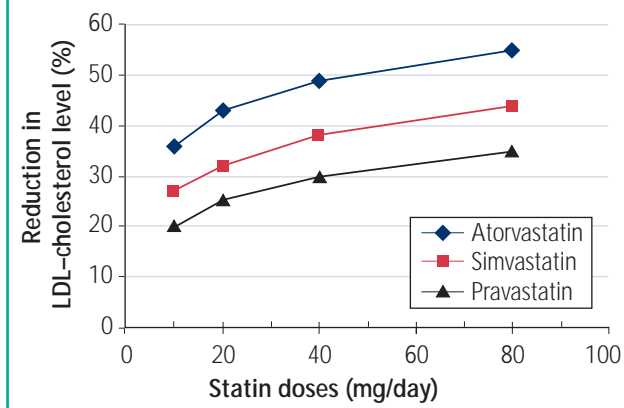
Atorvastatin is an HMG-CoA reductase inhibitor (statin) that lowers plasma cholesterol levels. Statins are first line for the treatment of hypercholesterolaemia.^{2,3} In patients with coronary heart disease and in others at high cardiovascular risk, statins reduce the risk of death, myocardial infarction, revascularisation or stroke.^{3,4} Aim for a target LDL-cholesterol level < 2.5 mmol/L (total cholesterol < 4.0 mmol/L).^{5-7*} Any step towards the target is likely to be beneficial.^{7,8}

Atorvastatin lowers cholesterol levels across its dose range

Atorvastatin is more potent at lowering cholesterol levels on a milligram-for-milligram basis compared with either simvastatin or pravastatin (see Figure 1).^{3,6,9} Similar reductions in cholesterol can be achieved with equipotent doses, but across its dose range atorvastatin reduces LDL-cholesterol about 5–20% more than the reductions achieved with simvastatin or pravastatin.

* Recommended for coronary heart disease, diabetes, stroke, transient ischaemic attack, peripheral vascular disease, microalbuminuria, renal disease, familial hypercholesterolaemia, 15% cardiovascular risk over 5 years, and in indigenous Australians.⁵⁻⁷

Figure 1: Percentage reduction in plasma LDL-cholesterol levels with recommended doses of atorvastatin, simvastatin and pravastatin^{6,9-11}



The dose equivalency of atorvastatin and simvastatin is reported to be between 1:2 (i.e. 10 mg is similar to 20 mg)^{6,9} and 1:4 (i.e. 10 mg is similar to 40 mg).¹¹ However, a meta-analysis that reported the equivalency of 1:4¹¹ did not assess potential differences between studies. Atorvastatin reduces plasma triglyceride levels more than simvastatin, and simvastatin elevates plasma HDL-cholesterol levels more than atorvastatin.⁹ The clinical significance of these differences is unknown.

Lowering cholesterol with atorvastatin, simvastatin or pravastatin reduces the risk of cardiovascular events

There are currently no head-to-head studies that directly compare the effectiveness of atorvastatin with equipotent doses of other statins for reducing the risk of cardiovascular events. The PROVE-IT¹² trial of intensive versus moderate lipid modification in acute coronary syndromes is the only head-to-head study comparing the clinical outcomes of statins. The absolute risk of a major cardiovascular event or death from any cause was reduced by 3.9% more with atorvastatin 80 mg (mean LDL-cholesterol 1.6 mmol/L) compared with pravastatin 40 mg (mean LDL-cholesterol 2.5 mmol/L).¹² This was largely due to reductions in revascularisation and unstable angina.¹²

Indirect comparison of atorvastatin, simvastatin and pravastatin using the clinical outcomes from placebo-controlled studies is difficult, as there are significant differences between the study populations.¹³⁻²⁴ [www](#) Statins provided greater absolute benefits in patients with a history of cardiovascular events (secondary prevention) compared with those without (primary prevention).^{4,8} In some studies, patients treated with placebo or 'usual care' were also prescribed lipid-lowering drugs, so differences between treatment groups were reduced.^{13-21,24} This predominantly occurred in the HPS¹³ (simvastatin) and ALLHAT-LLT¹⁸ (pravastatin) studies, where statins were prescribed on average in 17% of patients receiving placebo or 'usual care'.

Choose atorvastatin, simvastatin or pravastatin when initiating treatment with a statin.² If maximum recommended doses do not achieve treatment goals, switch to a statin that is more potent at lowering cholesterol (see Figure 1 and Dosing issues). Combining a statin with another lipid-modifying (non-statin) drug can also help reduce cholesterol.^{2,3,6}

Aggressively lowering cholesterol below the current recommended targets continues to be debated

In the Treating to New Targets (TNT) study²⁵, treatment with atorvastatin 80 mg daily (mean LDL-cholesterol 2.0 mmol/L) reduced the absolute risk of myocardial infarction and stroke by 1.3% and 0.8%, respectively, more than atorvastatin 10 mg daily (mean LDL-cholesterol 2.6 mmol/L). However, higher statin doses increase the risk of adverse effects (see Safety issues). Intensive lipid modification (mean LDL-cholesterol 1.6–2.0 mmol/L) with atorvastatin 80 mg or simvastatin 40 mg/80 mg did not reduce overall mortality compared with less intensive treatment (LDL-cholesterol 2.0–2.6 mmol/L).^{12,25-27} Studies were not powered to detect differences in mortality, thus the benefits are unclear. The threshold below which lowering of cholesterol becomes harmful, or has little added benefit, is unknown.

[www](#) Refer to this review at www.npsradar.org.au for more information on the effects of atorvastatin, simvastatin and pravastatin in placebo-controlled studies

Safety issues

Atorvastatin is well tolerated and its safety profile is similar to that of other statins.²⁸ Adverse effects include myalgia, mild gastrointestinal symptoms, elevated transaminase levels and headache.^{2,3} Rarely, myopathy or rhabdomyolysis can occur.³

Atorvastatin poses a similarly low risk of myopathy and rhabdomyolysis to that of other statins

Stop treatment with atorvastatin if patients develop persistent symptoms of muscle aches, mild to severe pain, or stiffness or weakness, even when plasma creatine kinase levels are normal.²⁹ Symptoms are usually reversible within a few days to weeks of stopping treatment.²⁹ Consider restarting atorvastatin at a lower dose after at least 4 weeks if symptoms were mild and when plasma creatine kinase levels have returned to normal.³ If the reaction recurs, stop atorvastatin permanently.³ An alternative statin may be considered but continue to monitor for signs of muscle toxicity.³

Studies have rarely reported myopathy or rhabdomyolysis with atorvastatin^{12,14,20,23,25,26} but these are strongly associated with certain risk factors (see Box 1). Patients most likely to develop muscle disorders, such as those with multiple comorbidities or taking interacting drugs, are usually excluded from statin trials and thus cases may have been underreported.

In 2004 the Adverse Drug Reactions Advisory Committee (ADRAC) reported that risk factors existed in nearly half of the cases of statin-induced myalgia, myopathy or raised plasma creatine kinase levels, and in more than 75% of cases of rhabdomyolysis.³⁰ A postmarketing analysis reported that simvastatin caused more adverse effects related to muscle than atorvastatin, but patients taking simvastatin on average received higher doses and more concomitant interacting drugs.³²

In the A to Z trial²⁷, 9 of 2263 patients developed muscle disorders (including three cases of rhabdomyolysis) with simvastatin 80 mg. Risk factors were evident in three cases and included renal failure, use of verapamil, or alcohol abuse. In the TNT study²⁵, although there were no reports

of elevated plasma creatine kinase levels (> 10 times upper limit of normal) or rhabdomyolysis related to atorvastatin 80 mg, 197 patients with adverse reactions to the 10 mg dose during the run-in phase (35 with myalgia) did not continue the study.

Box 1: Factors that increase the risk of muscle disorders with statins^{2,3,29-31}

High plasma levels of statins due to high doses

- 40 mg daily, particularly with other coexisting risk factors

Concomitant drugs that may increase plasma levels of statins by inhibiting CYP3A4 hepatic or gut metabolism*

- Calcium-channel blockers (diltiazem, verapamil)
- Macrolide antibiotics (clarithromycin, erythromycin)
- Azole antifungals (fluconazole, itraconazole, ketoconazole)
- SSRIs (fluvoxamine, fluoxetine)
- Protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)
- Others: amiodarone, cyclosporin, delavirdine, grapefruit juice

Concomitant drugs that may cause muscle damage

- Cyclosporin, gemfibrozil, fenofibrate, nicotinic acid

Concurrent illness or disease states

- Infection, trauma or major surgery
- Metabolic disorder (e.g. diabetes, hypothyroidism)
- Renal or hepatic disease
- Previous muscle damage with a statin

Patient demographics

- Older age (\geq 70 years), female gender, low body weight

* Does not apply to pravastatin, as it is not metabolised by CYP enzymes^{3,31}

Monitor liver transaminases with statins, particularly at high doses

Elevations in liver transaminase levels (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) with statins are dose dependent but uncommon and rarely develop into serious hepatic reactions (e.g. hepatitis, cholestatic jaundice).^{3,28} Stop atorvastatin if ALT and/or AST levels are persistently three or more times the upper limit of normal.³ Elevations usually resolve with a lower dose or alternative statin.^{3,14}

In studies, patients taking atorvastatin 80 mg daily had a 1–3% greater absolute risk of elevated liver transaminase levels (ALT and/or AST > 3 times the upper limit of normal) compared with placebo²⁶, pravastatin 40 mg¹² or atorvastatin 10 mg.²⁵

Dosing issues

Start with a low dose of atorvastatin and titrate if necessary to achieve treatment goals (dose range 10–80 mg once daily).³³ Measure the cholesterol level within 4 weeks of initiating atorvastatin, or after dose titration.³³ Higher doses (40–80 mg daily) may be required to reduce cholesterol levels by \geq 50%. Atorvastatin can be taken at any time of the day, with or without food.³³

Changing from other statins to atorvastatin

Before switching treatment to atorvastatin, check that the patient has been compliant with taking their statin treatment. Monitor the patient for adverse effects, which can occur when treatments change, especially if titrating atorvastatin to a higher dose (see Safety issues).³⁰

Information for patients

Advise patients that:

- atorvastatin can lower cholesterol more than other 'statin' drugs
- atorvastatin must be taken every day in conjunction with lifestyle changes such as diet and exercise
- the cost of atorvastatin to the patient is the same as for most other statins
- adverse effects of the muscle or liver are rare and more likely to occur if blood levels of atorvastatin are increased (e.g. interacting drugs)
- persistent muscle aches, mild to severe pain, or stiffness or weakness must be reported promptly, especially after any change in treatment.

Suggest or provide the Lipitor consumer medicine information (CMI) when prescribing or supplying atorvastatin.

References

1. Australian Government Department of Health and Ageing. Questions and Answers — Price change for atorvastatin (Lipitor) in the 1 August issue of the Schedule of Pharmaceutical Benefits. Canberra: Commonwealth of Australia, 2005. <http://www.seniors.gov.au/internet/wcms/publishing.nsf/Content/health-pbs-atorvastinqa> (accessed 23 August 2005).
2. Therapeutic Guidelines: Cardiovascular. Version 4. Melbourne: Therapeutic Guidelines Ltd, 2003.
3. Australian Medicines Handbook 2005.
4. National Prescribing Centre. Update on statins. MeReC Briefing. Liverpool: National Prescribing Centre, 2005. http://www.npc.co.uk/MeReC_Briefings/2004/briefing_no_28.pdf (accessed 4 May 2005).
5. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Reducing risk in heart disease 2004. Guidelines for preventing cardiovascular events in people with coronary heart disease. National Heart Foundation of Australia, 2004. http://www.heartfoundation.com.au/downloads/RRHD_fullguide_update_010405.pdf (accessed 2 September 2005).
6. New Zealand Guidelines Group. New Zealand Cardiovascular Guidelines. Evidence-based Best Practice Guidelines. Handbook for Primary Care Practitioners. Wellington: New Zealand Guidelines Group, 2005. [http://www.nzgg.org.nz/guidelines/0101/050624_CVD_Resource_\(Final\)_v5_for_printing_2.pdf](http://www.nzgg.org.nz/guidelines/0101/050624_CVD_Resource_(Final)_v5_for_printing_2.pdf) (accessed 2 September 2005).
7. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Med J Aust 2001;175:S57–S88.
8. Baigent C, et al. Lancet 2005;366:1267–78.
9. US Department of Veterans Affairs Pharmacy Benefits Management Strategic Healthcare Group. Drug Class Review: Hydroxymethylglutaryl-coenzyme A Reductase Inhibitors (statins). Washington DC, 2002.
10. Helfand M, et al. Drug Class Review on HMG-CoA Reductase Inhibitors (Statins). Drug Effectiveness Review Project. Portland: Oregon Health and Science University, 2005. <http://www.ohsu.edu/drugeffectiveness/reports/documents/Statins%20Final%20Report%20u3.pdf> (accessed 22 September 2005).
11. Law MR, et al. BMJ 2003;326:1423.
12. Cannon CP, et al. N Engl J Med 2004;350:1495–504.
13. Heart Protection Study Collaborative Group. Lancet 2002;360:7–22.
14. Athyros VG, et al. Curr Med Res Opin 2002;18:220–8.
15. Shepherd J, et al. Lancet 2002;360:1623–30.
16. Pedersen TR, et al. Lancet 1994;344:1383–9.
17. Sacks FM, et al. N Engl J Med 1996;335:1001–9.
18. Furberg CD, et al. JAMA 2002;288:2998–3007.
19. Tonkin A, et al. N Engl J Med 1998;339:1349–57.
20. Colhoun HM, et al. Lancet 2004;364:685–96.
21. Sever PS, et al. Lancet 2003;361:1149–58.
22. Shepherd J, et al. N Engl J Med 1995;333:1301–7.
23. Koren MJ, Hunninghake DB. J Am Coll Cardiol 2004;44:1772–9.
24. GISSI Prevenzione Investigators. Ital Heart J 2000;1:810–20.
25. LaRosa JC, et al. N Engl J Med 2005;352:1425–35.
26. Schwartz GG, et al. JAMA 2001;285:1711–8.
27. de Lemos JA, et al. JAMA 2004;292:1307–16.
28. Newman CB, et al. Am J Cardiol 2003;92:670–6.
29. Hamilton-Craig I. Aust Prescr 2003;26:74–5. <http://www.australianprescriber.com/magazines/vol26no4/pdfs/Hamilton-Craig.pdf> (accessed 2 September 2005).
30. Adverse Drug Reactions Advisory Committee. Risk factors for myopathy and rhabdomyolysis with the statins. Australian Adverse Drug Reactions Bulletin. Canberra: Adverse Drug Reactions Advisory Committee, 2004. <http://www.tga.gov.au/adraadrbaadr0402.pdf> (accessed 2 September 2005).
31. Hamilton-Craig I. Med J Aust 2001;175:486–9.
32. Alsheikh-Ali AA, et al. Circulation 2005;111:3051–7.
33. Pfizer Australia Pty Ltd. Lipitor Product Information, 29 March 2005.

Date prepared: September 2005

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

Anastrozole (Arimidex) for the treatment of hormone-dependent early breast cancer in postmenopausal women

(a-NASS-tra-zole)

Summary

- The PBS listing for anastrozole changed on 1 December 2005 to include all postmenopausal women with hormone-dependent early breast cancer.
- Choose anastrozole or tamoxifen as a first-line adjuvant treatment for hormone-dependent early breast cancer.
- Anastrozole may be preferable for women at high risk of endometrial cancer, thromboembolism, cerebrovascular events or metastatic disease.
- Continue adjuvant hormonal treatment for a total of 5 years.
- Anastrozole improves disease-free survival compared with tamoxifen, but there is currently no evidence that it improves overall survival.
- Anastrozole increases the risk of fracture compared with tamoxifen.

06

PBS listing

Anastrozole is listed on the PBS as a restricted benefit for the adjuvant treatment of hormone-dependent early or advanced breast cancer in postmenopausal women.¹ It is not PBS subsidised for primary prevention of breast cancer.¹

Reason for PBS listing

Anastrozole was previously listed on the PBS for postmenopausal women with hormone-dependent advanced breast cancer, or for postmenopausal women with hormone-dependent early breast cancer when tamoxifen was contra-indicated or not tolerated.¹

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended that the listing for anastrozole be extended to all postmenopausal women with hormone-dependent early breast cancer on the basis of acceptable cost effectiveness compared to tamoxifen.^{1,2} The PBAC accepted that the incremental cost is justified by the expected long-term survival benefits, which are in part due to the prevention of contralateral breast cancer.^{1,2}

Place in therapy

Anastrozole is a selective, nonsteroidal aromatase inhibitor that reduces the production of oestrogens in peripheral tissues.^{3,4} It inhibits tumour growth in postmenopausal women with hormone-dependent early (operable) or advanced (metastatic) breast cancer.^{3,4}

Tamoxifen is a selective oestrogen-receptor modulator that has been the standard adjuvant treatment for early breast cancer for many years.⁵⁻⁷ It inhibits the binding of oestrogen to receptor sites in tumours but has oestrogen-like effects on the endometrium, bone and lipids.^{3,7}

Use anastrozole or tamoxifen first line

Choose anastrozole or tamoxifen on an individual patient basis, weighing the potential absolute benefits against the possible harms of treatment.⁸ Continue adjuvant hormonal treatment for 5 years; longer treatment is the subject of ongoing studies.⁸

Evidence for anastrozole in hormone-dependent early breast cancer is based on the 5-year results of the ATAC trial, which involved 9366 postmenopausal women.⁹⁻¹¹ Anastrozole improved disease-free survival (time to local or distant recurrence, new primary breast cancer or death from any cause) compared with tamoxifen (relative risk reduction [RRR] 17%, 95% confidence interval [CI] 6% to 27%). Forty women need to be treated with anastrozole for 5 years, instead of tamoxifen, for one additional woman to remain disease-free during this time. There was no significant difference in overall survival between the anastrozole and tamoxifen groups after 5 years of follow-up.¹¹

The benefit-harm profile of tamoxifen in hormone-dependent early breast cancer has been established in meta-analyses of more than 80 000 women in randomised trials, many of whom were followed up for more than 15 years.⁵

Five-year treatment with tamoxifen reduced the relative risk of recurrence (local or distant recurrence or new primary breast cancer) by 41% (99% CI 33% to 49%) and breast cancer mortality by 34% (99% CI 24% to 44%) compared with no hormonal treatment.⁵

Tamoxifen increases the incidence of endometrial cancer, thromboembolism and stroke.^{5,6} However, it does not significantly increase the risk of death from these causes.^{5,6} The cumulative incidence of endometrial cancer with tamoxifen is small (0.1% per year) and is outweighed by a cumulative decrease in the incidence of new primary (contralateral) breast cancer (0.2% per year).⁵ Anastrozole increases the absolute risk of fracture compared with tamoxifen (see Safety issues).⁹⁻¹¹

Anastrozole may be preferred in some women

In the ATAC trial, anastrozole prolonged the time to distant recurrences compared with tamoxifen (RRR 16%, 95% CI 0% to 30%).¹¹ The incidence of contralateral breast cancer was also reduced by anastrozole compared with tamoxifen (RRR 53%, 95% CI 25% to 71%).¹¹ Distant recurrences are more common and incurable.¹² Anastrozole prevented many more distant recurrences than it did contralateral breast cancers when compared with tamoxifen.¹¹

There are, however, longer-term data on the use of tamoxifen as a first-line adjuvant treatment. The effect of tamoxifen persists for more than 15 years after initial diagnosis of breast cancer.⁵ Most of the effect on breast cancer mortality is seen after women have completed their 5 years of tamoxifen treatment (absolute risk reduction at 5 and 15 years, 3.6% and 9.2%, respectively).⁵ Long-term data beyond 5 years are currently unavailable for anastrozole.

Anastrozole is the drug of choice when tamoxifen is contra-indicated.⁸ It may be preferred for women at high risk of endometrial cancer, thromboembolism or cerebrovascular events.^{13,14} Anastrozole may also be preferred for some women at high risk of metastases.

Should women switch to anastrozole if they have remained disease free while taking tamoxifen?

There is evidence of benefit in starting anastrozole after 2 or 3 years of tamoxifen.^{15,16} However, long-term follow-up data on switching treatment are not yet available.

In the combined analysis of the ARNO 95 trial and ABCSG trial 8¹⁵, switching to anastrozole after 2 years of tamoxifen did not improve overall survival, but improved disease-free survival (time to local or distant recurrence or contralateral breast cancer) compared with 5 years of tamoxifen (RRR 40%, 95% CI 19% to 56%).

In the ITA trial¹⁶, anastrozole improved disease-free survival (time to local or distant recurrence) when initiated 2 or 3 years after tamoxifen, compared with 5 years of tamoxifen (RRR 65%, 95% CI 32% to 82%). This result may be greater than in other trials because it was a smaller trial and included women with a poorer prognosis (all node positive).¹⁶

Consider switching to anastrozole if longer treatment with tamoxifen poses an unacceptably high risk of adverse effects (see Safety issues). Start anastrozole no earlier than 2 or 3 years after starting tamoxifen, unless tamoxifen is not tolerated or disease recurs.⁸ Do not use anastrozole in combination with tamoxifen.⁹⁻¹¹

Safety issues

Anastrozole is generally well tolerated.^{3,4} Common adverse effects include hot flushes, asthenia or fatigue, nausea, headache and musculoskeletal disorders.^{3,4} Anastrozole may increase the risk of fracture compared with tamoxifen.^{3,4}

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online or by using the 'Blue Card' distributed with the *Schedule of Pharmaceutical Benefits* and *Australian Prescriber* journal. For information about adverse drug reaction reporting, see the Therapeutic Goods Administration website (www.tga.gov.au).

Anastrozole and tamoxifen have different risks of adverse effects

In the ATAC trial the most common adverse effects reported with anastrozole or tamoxifen were hot flushes, nausea and vomiting, fatigue or tiredness, mood disturbances and arthralgia.^{9–11} Drug-related serious adverse effects were less frequent with anastrozole than with tamoxifen (4.7% vs 9.0%, respectively).¹¹ There were fewer discontinuations due to drug-related adverse effects with anastrozole than with tamoxifen (6.5% vs 8.9%).¹ However, the drugs differ in their absolute risks for individual adverse effects (Table 1).¹¹

Tamoxifen causes a greater incidence of thromboembolism and endometrial cancer because of its partial oestrogen-like activity.³ However, this action also protects against bone loss.^{3,5} Anastrozole decreases circulating oestrogen levels, which can increase the risk of fracture relative to that for tamoxifen.³ Anastrozole is not associated with the oestrogen-like adverse effects of tamoxifen.³

Use anastrozole with caution in women with osteoporosis or a history of fracture

Monitoring bone mineral density is recommended before and during treatment with anastrozole.^{3,4,8} Prophylaxis or treatment of bone loss may be necessary.^{4,8} The long-term increased risk of fracture with anastrozole, particularly of the hip, is currently unknown.⁸ However, in the ATAC trial there was no significant difference in the incidence of hip fracture between anastrozole and tamoxifen (1.2% vs 1.0%, respectively)¹¹ and total fracture rates returned to baseline levels after treatment with anastrozole was completed.¹

Dosing issues

The recommended dose of anastrozole is one 1 mg tablet taken once daily.^{3,4} Continue treatment for 5 years in postmenopausal women with early breast cancer.^{3,4,8}

Table 1: Absolute risk of adverse events reported with anastrozole and tamoxifen in the ATAC trial^{1,11}

Adverse events*	Anastrozole (%)	Tamoxifen (%)	Difference with anastrozole (%)
Hot flushes	35.7	40.9	-5.2
Arthralgia	35.6	29.4	+6.2
Fractures†	11.0	7.7	+3.3
Vaginal discharge	3.5	13.2	-9.7
Vaginal bleeding	5.4	10.2	-4.8
Hysterectomy	1.2	4.7	-3.5
Venous thromboembolic events	2.8	4.5	-1.7
Ischaemic cerebrovascular events	2.0	2.8	-0.8
Endometrial cancer	0.2	0.8	-0.6

* Reported during 5-year treatment or within 14 days of discontinuation † Included hip, spine, wrist/Colles or other fracture

Information for patients

Inform patients that anastrozole:

- is an additional hormonal treatment for early breast cancer in postmenopausal women who have hormone receptors in the cancer cells
- may be suitable for women at increased risk of endometrial cancer, blood clots or stroke, which occur rarely with tamoxifen
- may prolong the time to a recurrence of cancer and prevent more new cancers in the opposite breast compared with tamoxifen
- has not yet been proven to improve overall survival compared with tamoxifen
- causes more musculoskeletal pain and increases the risk of fracture relative to that for tamoxifen.

To help prevent bone loss and reduce the risk of fracture, advise patients to¹⁷:

- have an adequate dietary intake of calcium and vitamin D
- undertake regular exercise that includes resistance training, to improve muscle mass, strength and balance
- stop smoking and limit alcohol intake.

Refer patients to the National Breast Cancer Centre's guideline for women with early breast cancer, available at www.nbcc.org.au/resources/documents/EBC_earlyguide.pdf

Suggest or provide the Arimidex consumer medicine information (CMI) when prescribing or supplying anastrozole.

References

1. Australian Government Department of Health and Ageing. Public summary document. Anastrozole, tablets, 1 mg, Arimidex, July 2005. Canberra: Commonwealth of Australia, 2005. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-anastrozole> (accessed 4 November 2005).
2. Australian Government Department of Health and Ageing. July 2005 PBAC Outcomes — Positive Recommendations. Canberra: Commonwealth of Australia, 2005. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-jul05-positive#anas> (accessed 11 October 2005).
3. Australian Medicines Handbook 2005.
4. AstraZeneca Pty Ltd. Arimidex Product Information. 1 August 2005.
5. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 2005;365:1687–717.
6. Early Breast Cancer Trialists' Collaborative Group. *Cochrane Database Syst Rev* 2001:Issue 1. Art. No.: CD000486. <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000486/pdf/fs.html> (accessed 11 October 2005).
7. Hardman J, et al. A. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. 10th edn. USA: The McGraw-Hill Companies, Inc, 2001.
8. Winer EP, et al. *J Clin Oncol* 2005;23:619–29.
9. Baum M, et al. *Cancer* 2003;98:1802–10.
10. Baum M, et al. *Lancet* 2002;359:2131–9.
11. Howell A, et al. *Lancet* 2005;365:60–2.
12. National Institute for Clinical Excellence. *Improving outcomes in breast cancer: manual update. Guidance on Cancer Services*. London: NICE, 2002. http://www.nice.org.uk/pdf/Improving_outcomes_breast_cancer_manual.pdf (accessed 27 October 2005).
13. Prescrire editorial team. *Prescrire Int* 2005;14:108–10.
14. Prescrire editorial team. *Prescrire Int* 2005;14:43–4.
15. Jakesz R, et al. *Lancet* 2005;366:455–62.
16. Boccardo F, et al. *J Clin Oncol* 2005;23:5138–47.
17. O'Neill S, et al. *Aust Fam Physician* 2004;33:910–7. <http://www.racgp.org.au/afp/downloads/pdf/november2004/20041031oneill.pdf> (accessed 15 November 2005).

Date prepared: October 2005

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

Buprenorphine transdermal patches (Norspan) for chronic severe pain

(bu-pre-NOR-fun)

Summary

- Transdermal buprenorphine could be considered in chronic severe pain when lower doses of strong opioids are indicated. However, more familiar opioids such as morphine are preferred and offer a broader range of doses and formulations.
- Buprenorphine produces typical opioid adverse effects (constipation, headache, nausea, vomiting, dizziness).
- Avoid prescribing buprenorphine to people who may be dependent on other opioids because it can precipitate withdrawal symptoms, including pain.

PBS listing

Restricted benefit

Chronic, severe disabling pain not responding to non-opioid analgesics.

Authorities for increased maximum quantities will be available for patients meeting the criteria listed in the note in the *Schedule of Pharmaceutical Benefits*. See *NPS RADAR 'In Brief'*, August 2005, for details.

Buprenorphine is a schedule 8 substance and so must be prescribed in accordance with State or Territory regulations (see www.tga.gov.au/ndpsc/stdpu.htm).

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended listing on the basis of similar safety, efficacy and cost to those for oxycodone hydrochloride controlled-release tablets (i.e. cost minimisation).¹ Buprenorphine transdermal patch and oxycodone controlled-release tablets have not been directly compared in clinical trials, so the economic analysis was based on an indirect comparison using immediate-release oxycodone plus paracetamol combination tablets and placebo as common comparators. For the purposes of the cost-minimisation analysis, the equi-effective doses were transdermal buprenorphine 5 mg (releasing buprenorphine 5 micrograms per hour), 10 mg (10 micrograms per hour) and 20 mg (20 micrograms per hour) every 7 days equivalent to oxycodone controlled release 10 mg, 20 mg and 30 mg twice daily, respectively.

Place in therapy

Transdermal buprenorphine may be used in chronic severe pain when lower doses of strong opioids are indicated. However, the place of transdermal buprenorphine in pain management is not well established. More familiar and better-studied opioids such as morphine are preferred and provide a broader range of doses and formulations. The 7-day patch formulation may have a particular role for patients who are vomiting or have swallowing difficulties. The patches are the only transdermal opioid preparation listed on the PBS for non-malignant pain.

Transdermal buprenorphine patches deliver buprenorphine at a constant rate over 7 days. The dose equivalence of transdermal buprenorphine and oral morphine is not established. The manufacturer suggests that the dose range covered by the three patch strengths may be equivalent to oral morphine up to 90 mg/day.² Other literature and the dose relativities suggested for the higher-strength patches available overseas indicate that the buprenorphine 20-microgram-per-hour patch might be equivalent to oral morphine up to 36 mg/day or 53 mg/day³; however, published evidence for equi-analgesic doses is sparse and of low quality so it cannot be regarded as definitive.

There is little information available about the efficacy and tolerability of buprenorphine patches in comparison with other strong opioids because none of the studies assessing the efficacy and safety of the patches available in Australia has been published. Results of trials using the higher-strength buprenorphine patches available

overseas cannot be reliably extrapolated to the patches available in Australia. The manufacturer's submission for PBS listing mentions several trials comparing transdermal buprenorphine with either oxycodone plus paracetamol combination tablets, buprenorphine sublingual tablets or hydrocodone plus paracetamol combination tablets in people with osteoarthritis or chronic back pain.* These studies found no significant differences in analgesic efficacy between buprenorphine and the comparators.⁴

Transdermal buprenorphine is not suitable for the management of acute pain because it has a slow onset and extended duration of action.

Buprenorphine: a partial agonist

Buprenorphine is a partial agonist so there is a ceiling dose to its analgesic effect — that is, above a certain dose there is no further analgesic effect. The dose at which this occurs in humans is not established but it is unlikely at the doses in the transdermal patches.

Because of its partial agonist activity, buprenorphine may trigger opioid withdrawal symptoms in people who have developed physical dependence on other opioids.

Buprenorphine has high affinity for *mu* opioid receptors and is not easily displaced by opioid antagonists. Consequently, the effects of buprenorphine in overdose are only partially reversed by naloxone.

Include non-drug treatment in managing pain

Pain management should involve a range of treatment modalities with an emphasis on non-drug treatment. Non-drug treatments may include those directed at improving physical function (such as exercise and physiotherapy), psychological wellbeing (such as cognitive behavioural therapy and stress management) and encouraging return to normal activity.^{5–7}

Ensure that patients understand the goals of treatment and have realistic expectations. It is usually not possible to eliminate pain completely. In chronic non-cancer pain, the goal of treatment is to maintain or restore function and improve quality of life as well as to provide pain relief.⁵ In cancer pain, providing pain relief is the primary goal.

*Doses were oxycodone with paracetamol 5 mg/325 mg 1–3 tablets 4 times daily, buprenorphine sublingual tablets 200 micrograms or 400 micrograms 6–8-hourly and hydrocodone with paracetamol 2.5 mg/250 mg 1–3 tablets 4 times daily.

A written pain-management plan helps to ensure that all members of the healthcare team take a consistent approach to the patient's pain management and helps patients take an active role in managing their own pain.⁶

Chronic non-cancer pain: consider an opioid when other analgesics are inadequate

A stepwise approach is appropriate, starting with non-opioids. Paracetamol is the drug of choice in mild to moderate pain. Add or substitute a nonsteroidal anti-inflammatory drug if paracetamol is inadequate. Consider adding or substituting a weak opioid (codeine or tramadol) if the patient does not respond to non-opioids.⁶ Encourage regular (rather than as-needed) use of analgesics and titrate to maximum doses before moving to the next step.⁶

Strong opioids (such as morphine, oxycodone and buprenorphine) should only be considered for patients who do not respond to other treatments. Before opioids are prescribed, the potential benefits should be weighed against the possibility of adverse effects and misuse. Consider whether the patient should be assessed by a specialist pain team before opioids are started.

Published clinical trial evidence for opioids in chronic non-cancer pain is scarce, so guidelines for opioid prescribing rely largely on clinical experience and consensus.

For more information, see the NSW Therapeutic Advisory Group's *General principles: rational use of opioids in chronic or recurrent non-malignant pain*.⁶

Cancer pain: buprenorphine patches less suitable

The transdermal buprenorphine patch available in Australia has not been evaluated in cancer pain. Other opioids are more suitable in cancer pain because there is extensive experience with them and they provide a greater choice of dose forms and larger dose range to control severe cancer pain.

Safety issues

Buprenorphine produces typical opioid adverse effects (such as constipation, headache, nausea, vomiting, dizziness). Local irritation may occur at the application site.

Buprenorphine has a long half-life, so plasma concentrations fall slowly after the patch is removed. Another opioid should not be started within 24 hours of removing a patch.⁸

Dependence and abuse potential

Physical dependence may develop with chronic use of buprenorphine. If a withdrawal syndrome does occur when buprenorphine is discontinued, it is usually of mild to moderate intensity, occurs within 2 days and resolves within 2 weeks.^{8,9}

Avoid prescribing buprenorphine to people who may be dependent on other opioids because it can precipitate withdrawal symptoms, including pain. The severity of the withdrawal syndrome will depend on the degree of physical dependence and the dose of buprenorphine given.⁸

Transdermal buprenorphine may have lower abuse potential than other buprenorphine dosage forms because of the relatively low plasma concentrations achieved, the slow onset of effect and because it is likely to be difficult to extract the drug from the matrix design. Misuse could take the form of using excessive amounts of the intact patch or applying it to sites that would enhance systemic absorption. It should be used with caution in people with a past history of dependence on alcohol or other drugs.

Overdose: effects only partially reversed by naloxone

In overdose the effects of buprenorphine are only partially reversed by naloxone.⁹ The manufacturer states that the dose of naloxone should start in the usual range but that naloxone 5–12 mg intravenously may be required.⁸ Repeated naloxone doses may be needed because naloxone has a shorter duration of action than buprenorphine. Management of overdose should focus on maintaining adequate ventilation.⁹

There is likely to be a lower risk of overdose with buprenorphine patches than with other dose forms (sublingual tablets and injection) because the doses administered via the patches are much lower.

The respiratory depressant effects of buprenorphine are subject to a ceiling effect. However, significant respiratory depression has been reported with buprenorphine, particularly when it is administered intravenously. Deaths have been associated with very high doses or inappropriate use of buprenorphine (such as crushing and injecting sublingual tablets) in combination with benzodiazepines or other central nervous system depressants.⁹

Dosing issues

Buprenorphine patches are available in three strengths: 5 micrograms per hour, 10 micrograms per hour and 20 micrograms per hour.

Opioid-naïve patients should start at the lowest strength. Supplemental analgesics should be continued as needed during titration because buprenorphine concentrations rise slowly. Patients converting from other opioids (up to the equivalent of oral morphine 90 mg/day) can also begin on a low strength of buprenorphine and should continue with their previous regimen during titration.⁸

Use non-opioid analgesics for breakthrough or incident pain.⁵ In clinical trials, simple analgesics (such as paracetamol with or without codeine) were used when additional analgesia was required.

The dose should be titrated to effect and should not be increased at intervals of less than 3 days. To increase the dose, remove the current patch and apply a higher-strength patch or a combination of 2 patches. No more than two 20-microgram-per-hour patches should be used at once. The patches should not be cut because this may compromise the accuracy of dosing.

New patches should always be applied to a different site from the previous one. Any site should not be re-used for 3–4 weeks to minimise the risk of local skin irritation and because immediately re-using a site can increase the rate of absorption of buprenorphine.

The Norspan product information contains detailed instructions for applying patches.

Information for patients

Ensure that patients understand how to correctly use and dispose of buprenorphine patches.

Detailed information about applying the patch is given in the Norspan consumer medicine information (CMI). An illustrated leaflet explaining patch application is available from the manufacturer, Mundipharma Pty Ltd (ph 1800 188 009).

In particular, patients should be advised:

- not to apply a new patch to the same application site for 3–4 weeks to reduce the chances of local skin irritation
- that the patch does not need to be applied to the site of the pain. It should be applied to a nearly hairless site on the upper outer arm, upper chest, side of the chest or upper back
- to avoid exposing the application site to heat (such as electric blankets, saunas, heat lamps or intensive sunbathing) because this may increase the level of buprenorphine in their blood and increase the risk of adverse effects
- to speak to their doctor if they are using the patch during a severe fever, because this may also increase blood buprenorphine levels. Using the patch during mild fever is unlikely to affect the level of buprenorphine in their blood
- to fold used patches in half (with the sticky sides together) and dispose of them out of reach of children.

Discuss the potential adverse effects of buprenorphine. Most adverse effects reduce with time. Constipation may persist; advise patients to drink adequate amounts of water, increase their fibre intake and remain as mobile as possible. Regular laxatives (combined stool softener with stimulant laxative, such as Coloxyl with Senna, or an osmotic laxative, such as sorbitol or lactulose) should be started when buprenorphine is initiated and continued for long as buprenorphine or other opioids are used.

References

1. Pharmaceutical Benefits Advisory Committee. July 2005 PBAC Outcomes — Positive Recommendations. Canberra: Australian Government Department of Health and Ageing; 19 August 2005. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-jul05-positive> (accessed 28 October 2005).
2. Mundipharma Pty Ltd. Norspan (buprenorphine transdermal patch): pre-subcommittee response, July 2005 PBAC meeting. 2005.
3. Sittl R, et al. *Clin Ther* 2005;27:225–37.
4. Personal communication, Australian Government Department of Health and Ageing and Mundipharma Pty Ltd.
5. Australian Medicines Handbook 2005.
6. NSW Therapeutic Assessment Group. General principles: rational use of opioids in chronic or recurrent non-malignant pain. 2002. <http://www.ciap.health.nsw.gov.au/nswtag/publications/guidelines/GeneralPrinciples4=12=02.pdf> (accessed 18 August).
7. Analgesic Writing Group. Therapeutic Guidelines: Analgesic. Version 4. North Melbourne: Therapeutic Guidelines Pty Ltd, 2002.
8. Mundipharma Pty Ltd. Norspan transdermal patch product information. 4 April 2005.
9. Johnson RE, et al. *J Pain Symptom Manage* 2005;29:297–326.

Date prepared: August 2005

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

In Brief

In Brief is a digest of news items about NPS RADAR, new drugs and changes to PBS listings.

High-strength fluticasone inhalers remain PBS listed

The 250-microgram-strength fluticasone aerosol metered-dose inhaler (Flixotide CFC-Free) and the 500-microgram-strength fluticasone dry powder inhaler (Flixotide Accuhaler) continue to be listed on the Pharmaceutical Benefits Scheme. Rather than removing these two products from the *Schedule of Pharmaceutical Benefits*, as was previously announced, the supplier (GlaxoSmithKline) applied for an altered listing.

As of 1 August 2005 the maximum number of PBS repeats for these two products was reduced from 5 to 1.

Pethidine to be deleted from doctor's bag supplies

Pethidine will not be available through the 'Emergency drug (doctor's bag) supplies' provision in the *Schedule of Pharmaceutical Benefits* from 1 April 2006.¹ This change has occurred because pethidine has several significant disadvantages compared with other opioids. Other opioids are preferred because pethidine:²⁻⁴

- has a short duration of action and is no more effective than other opioids
- has similar adverse effects to those of morphine, including increased biliary tract pressure
- is metabolised to norpethidine, which may cause serious adverse effects, such as seizures, particularly in renal impairment
- can cause serotonin syndrome when combined with other serotonergic drugs, such as selective serotonin re-uptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs)
- is more likely than other opioids to be abused by patients and health professionals.

Morphine injection is preferred for severe acute pain and is available as a doctor's bag item. Tramadol injection is also available as a doctor's bag item but has a more limited role; it may be a useful alternative for people with moderate pain who cannot tolerate conventional

opioids or who are at particular risk of opioid-induced respiratory depression. Note that tramadol shares some of the disadvantages of pethidine: it may cause seizures (particularly when combined with other drugs that lower the seizure threshold) and can trigger serotonin syndrome when used in high doses or with other serotonergic drugs.^{5,6}

Pethidine will continue to be available on an individual patient basis as a restricted benefit for the short-term treatment of acute pain.

References

1. Pharmaceutical Benefits Advisory Committee. July 2005 PBAC outcomes — positive recommendations. Canberra: Australian Government Department of Health and Ageing. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-jul05-positive> (accessed 19 October 2005).
2. Kaye KI, et al. *Med J Aust* 2005;183:129–33.
3. Davis S. Use of pethidine for pain management in the emergency department: a position statement of the NSW Therapeutic Advisory Group. Darlinghurst: NSW TAG, August 2004. <http://www.clininfo.health.nsw.gov.au/nswtag/publications/posstats/Pethidinefinal.pdf> (accessed 19 October 2005).
4. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence (2nd edn). Melbourne: ANZCA, 9 June 2005. <http://www.anzca.edu.au/publications/acutepain.htm> (accessed 19 October 2005).
5. Boyd I. *Med J Aust* 2005;182:595–6.
6. Hall M, Buckley N. *Aust Prescr* 2003;26:62–3.

Changes to narcotic analgesic prescribing on PBS in April 2006

Changes to PBS prescribing of narcotic analgesics were introduced in April 2005 and relate to obtaining a PBS authority to prescribe increased quantities or repeats of hydromorphone, methadone, morphine or oxycodone for severe disabling pain. The changes were outlined in the 'In Brief' section of the August 2005 issue of *NPS RADAR*¹ and will also apply to the 1 December listing of buprenorphine patches for severe disabling pain.

From 1 April 2006, the criterion that allowed patients whose narcotics were started in hospital before April 2005 to be prescribed increased quantities or repeats under PBS authority will be deleted. This means that prescribers will need to ensure that a pain management review has been conducted by a second medical practitioner to confirm continued clinical need and avoid potential interruption to the patient's continuing PBS supply of narcotic analgesic.

The pain management review needs to have been conducted within the 3 months preceding the date of the PBS authority request.

The criterion relating to initiation of narcotic treatment in a hospital is the only criterion being removed; all other changes introduced in April 2005 remain. However, Medicare Australia (formerly the Health Insurance Commission) advise that experience since the changes were introduced has revealed some confusion among prescribers applying for PBS authorities for increased quantities or repeats of narcotic analgesics.

It is intended that the PBS authority requests progress through the different criteria of the restriction such that:

- the initial PBS authority request applies when the total duration of narcotic analgesic treatment is less than 12 months
- should the treatment exceed 12 months, a subsequent application is required to extend the supply beyond 12 months; it is this application that requires the details of a pain management review conducted within the preceding 3 months
- then, if treatment continues and further supply is needed, this subsequent application does not require a pain management review; a review only needs to be demonstrated the first time use will exceed 12 months. Nonetheless, applications for treatment that extends beyond 12 months can only be approved if a PBS authority for narcotic analgesic treatment beyond 12 months was previously approved for that patient after a review of the management was provided by another practitioner (possibly another doctor from the same practice).

Reference

1. National Prescribing Service. PBS narcotic authority recommended. NPS RADAR August 2005. <http://www.npsradar.org.au/site.php?page=1&content=/npsradar/content/latestnews.html#aug05> (accessed 15 Nov 2005).

Benzodiazepines and NSAIDs added to PBS palliative care list

A new section for palliative care medicines on the PBS was introduced into the *Schedule of Pharmaceutical Benefits* in February 2004.

From 1 December 2005 the following agents have been added to this section for use in palliative care patients:

- some nonsteroidal anti-inflammatory drugs (NSAIDs) as adjuncts for severe pain, including diclofenac, ibuprofen, indomethacin, naproxen and sulindac
- nitrazepam and temazepam for insomnia
- diazepam and oxazepam for anxiety.

All palliative care listings are authority required.

Prescribers can request an initial authority to provide for a maximum of 4 months' therapy for palliative care patients. When continued therapy is required, authority approvals for subsequent prescriptions will be for a maximum of 1 month's supply only, unless the prescriber consults with a palliative care specialist or palliative care service, in which case up to 4 months' supply may be requested.

For full details of brand names, forms, strengths, and conditions of use, consult the Palliative Care Section (designated by mauve pages) of the *Schedule*.

More information about PBAC decisions now available

Ever wondered why a medicine gets listed on the PBS — or why it doesn't? The outcomes of Pharmaceutical Benefits Advisory Committee meetings have been available on the Department of Health and Ageing website for several years, but new information about that decision making is now available to all.

The reasons for all PBAC decisions — both positive recommendations to list on the PBS and negative recommendations — are now described in a 'public summary document' (PSD). Each PSD includes relevant information about the clinical and economic data presented to PBAC, as well as estimates of the PBS usage, which are considered by the Committee in making their recommendation. There is also a comment from the manufacturer about the PBAC decision.


The first PSDs published describe the decisions from the PBAC meeting in July. In general the PSDs from the March, July and November PBAC meeting cycle will be published around the end of June, October and February, respectively.

PSDs are published on the Department of Health and Ageing website.¹

Reference

1. Australian Government Department of Health and Ageing. PBAC Outcomes and Public Summary Documents. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-outcomes-and-public-summary-documents> (accessed 15 Nov 2005).

New web extras

Look out for the new web extra icon  in reviews on the *NPS RADAR* website. The icon can be found in the text and the navigation menu to direct you to extra relevant content. In this issue, the review 'Atorvastatin (Lipitor) for the management of lipid disorders' is supplemented by a web extra that summarises studies comparing the effects of statins and placebo or usual care on cholesterol levels and coronary event risk. Other web extras provide useful practical information, such as details of intolerance and contra-indications to metformin that may warrant prescribing rosiglitazone (see 'Rosiglitazone (Avandia) for type 2 diabetes mellitus').



***NPS RADAR* in your prescribing software**

NPS RADAR reviews are available on general practitioner desktops in major prescribing packages — Genie, Locum, Medical Director, and IBA Spectrum Plexus.

Every time you update your prescribing software, you'll be updating your new drugs information. Because of lead-in times, some reviews may be published online before they are available in your software.

You can find *NPS RADAR* by:

- Clicking on the *NPS RADAR* button at the bottom of your prescribing screen when you're selecting a medicine to prescribe; or
- Going to the *NPS RADAR* browser in your prescribing software any time you wish to look up new drug information.

If you have Medical Director or Locum, look for *NPS RADAR* under the Resources menu.

If you have Plexus, look in the Reference menu.

Or, if you have Genie, look under 'Open'.

Index of *NPS RADAR* reviews December 2004 – December 2005

The following *NPS RADAR* reviews are available on our website, www.npsradar.org.au. Look for the *NPS RADAR* index in **Quick Links**.

Angiotensin II receptor antagonists — unrestricted PBS listing	August 2005
Ciclesonide (Alvesco) inhaler for asthma	August 2005
Elevated cardiovascular risk with NSAIDs?	August 2005
Galantamine (Reminyl) prolonged-release capsules for dementia in Alzheimer's disease	December 2004
Methylphenidate (Ritalin) for attention deficit hyperactivity disorder	August 2005
Metformin/glibenclamide (Glucoavance) for type 2 diabetes mellitus	December 2005
Orlistat (Xenical) over-the-counter for obesity	December 2004
Pimecrolimus (Elidel) cream for facial atopic dermatitis in children	April 2005
Quinine (Quinate, Quinbisul, Quinsul) for muscle cramp	December 2004
Risperidone (Risperdal) for behavioural disturbances in dementia	April 2005
Rosiglitazone (Avandia) for type 2 diabetes mellitus	August 2005
Selective serotonin re-uptake inhibitors in child and adolescent depression	April 2005
Sertraline (Zoloft), fluoxetine (Lovan, Prozac) for premenstrual dysphoric disorder	December 2004

Visit www.npsradar.org.au to view all *NPS RADAR* reviews or register for email updates. *NPS RADAR* reviews are also available in GP prescribing software (Genie, IBA Spectrum Plexus, Locum and Medical Director).