

Timely, independent information about new drugs

**Lumiracoxib (Prexige) for osteoarthritis**

New PBS listing August 2006

01

**Alendronate with cholecalciferol (vitamin D<sub>3</sub>) (Fosamax Plus) for osteoporosis**

New PBS listing August 2006

06

**Fentanyl patches (Durogesic) for chronic pain**

Expanded PBS listing August 2006

12

**Moxonidine (Physiotens) for hypertension**

New PBS listing August 2006

18

**Adrenaline autoinjector (EpiPen) for acute allergic anaphylaxis**

Change in PBS listing August 2006

21

**In Brief**

Change of perindopril (Coversyl) salt from erbumine to arginine — New vaccine for pertussis, diphtheria and tetanus (Adacel) — Medicines listed on the PBS for Indigenous Australians — New drugs added to palliative care list — Ferrous fumarate 310 mg with folic acid 300 micrograms tablets (Ferro-F-Tab) unrestricted listing — Pseudoephedrine on prescription — Pioglitazone (Actos) and rosiglitazone (Avandia) authority wording changed

26



Rational Assessment of Drugs and Research

***NPS RADAR* provides timely, independent, evidence-based information on new drugs, research and PBS listings for general practitioners, specialists, pharmacists and other health professionals.**

The proliferation of combination products is an emerging quality use of medicines issue. Should therapy be initiated with a combination product? If not, when do patients need to progress to a combination? Can drug doses be titrated appropriately? Are combination products as much about marketing and positioning as they are about therapeutic synergies?

Invariably combination products are christened 'Brand Plus' to gain leverage off the parent drug's name and recognition. But are there any minuses to products called 'Plus'?

Alendronate (Fosamax) has been available through the PBS for many years for patients with established osteoporosis and previous fracture due to minimal trauma. In this setting, alendronate is cost effective in reducing the risk of subsequent fractures. From 1 August a combination of alendronate with cholecalciferol (vitamin D<sub>3</sub>) is available on the PBS for the same indication; the new combination is called Fosamax Plus.

The impulse might be to transfer patients currently treated with alendronate alone to the new combination. But identifying those who would benefit from this combination is not straightforward.

The vitamin D content of Fosamax Plus is inadequate to address vitamin D deficiency (see *NPS RADAR* review on p.6). Patients with normal vitamin D concentrations do not need supplementation, and those who are truly deficient need a higher,

therapeutic dose of vitamin D. Moreover, vitamin D supplementation did not demonstrate a significant effect on fractures in results from the Womens' Health Initiative study published recently.

A problem of a different form related to combination products has come to light with a relatively innocuous change in the formulation of perindopril (Coversyl) tablets. The perindopril salt has been changed from erbumine to arginine, resulting in changes in dose strength, tablet appearance and packaging, but without a change in product name. If switching patients from Coversyl to the combination product, Coversyl Plus (perindopril/indapamide), be aware that the two products have different strengths of perindopril (5 mg and 4 mg, respectively), and this may confuse some patients. A detailed description of this change can be found in the news section, *In Brief*, on p.26.

Lastly, the first COX-2 selective NSAID to become available in Australia in the post-Vioxx era is listed on the PBS for osteoarthritis from 1 August. Lumiracoxib (Prexige) can be prescribed on the PBS. The cardiovascular risk associated with NSAIDs remains under intense scrutiny, with new evidence and re-analyses of old evidence being churned out relentlessly. The review of lumiracoxib on p.1 outlines the potential gastrointestinal benefits and cardiovascular harms, as evidenced by the large TARGET study, and discusses where this new medicine might fit among the analgesic options for osteoarthritis.

**Timely, independent information about new drugs**

## **National Prescribing Service Limited**

National Prescribing Service Limited (NPS) is an independent, non-profit organisation for Quality Use of Medicines. We provide accurate, balanced, evidence-based information and services to help people choose if, when and how to use medicines to improve their health and wellbeing. We are member-based and work in partnership with health professionals, government, pharmaceutical industry and consumers. NPS is funded by the Australian Government Department of Health and Ageing.

## Lumiracoxib (Prexige) for osteoarthritis

(loo-MEE-rah-cox-ib)

### Summary

- Lumiracoxib is an alternative to other NSAIDs for managing pain in osteoarthritis. Paracetamol remains first line.
- Lumiracoxib is a COX-2 selective NSAID. Some trials of COX-2 selective NSAIDs have found an increase in the risk of cardiovascular events compared with placebo or with naproxen. Evidence for the long-term cardiovascular safety of lumiracoxib is limited.
- Lumiracoxib is contraindicated in patients with established cardiovascular disease and should be prescribed with caution for patients with significant cardiovascular risk factors.
- Lumiracoxib causes fewer serious ulcer complications than naproxen or ibuprofen, but should be used with caution in people with gastrointestinal risk factors.
- Use lumiracoxib for the shortest possible time. Try intermittent use for symptomatic relief of exacerbations or before painful activities.
- As with all NSAIDs, use lumiracoxib with caution in people with renal dysfunction, heart failure, oedema and hypertension. Lumiracoxib is contraindicated in severe renal dysfunction.

### PBS listing

#### Restricted benefit

Lumiracoxib 200 mg tablets are PBS listed for symptomatic treatment of osteoarthritis.

The other indications registered with the Therapeutic Goods Administration — acute pain and primary dysmenorrhoea — are not PBS subsidised. Lumiracoxib is not indicated for rheumatoid arthritis.

#### Reason for PBS listing

Lumiracoxib was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) on a cost-minimisation basis compared with celecoxib.<sup>1,2</sup> The PBAC agreed that lumiracoxib 200 mg was shown to be as effective as celecoxib 200 mg in treating the symptoms of osteoarthritis.

The PBAC was concerned about making another COX-2 selective NSAID widely available, in light of concerns about cardiovascular risks associated with this group of drugs.<sup>1</sup> It considered that caution in prescribing lumiracoxib was warranted, given the uncertainty regarding risk versus benefit for COX-2 selective NSAIDs.<sup>1</sup>

### Place in therapy

Lumiracoxib is a COX-2 selective NSAID. Several COX-2 selective NSAIDs have been shown to increase the risk of cardiovascular events compared with placebo and naproxen. Evidence about the cardiovascular safety of lumiracoxib is limited. Avoid lumiracoxib in patients at high cardiovascular risk. When symptoms cannot be managed with non-drug therapy and paracetamol alone, lumiracoxib is as effective as other NSAIDs in reducing symptoms of osteoarthritis and has a similar adverse-effect profile. As with other COX-2 selective NSAIDs, lumiracoxib is likely to be most useful for individuals at increased risk of gastrointestinal complications, although the possibility of ulcer complications remains high in these patients.

#### Paracetamol is first-line drug therapy for most patients with osteoarthritis

Paracetamol is effective in osteoarthritis and has a superior safety profile to that of NSAIDs.<sup>3</sup> Ensure that the dose is adequate (up to 4 g/day). Toxicity at therapeutic doses is extremely rare; paracetamol should be avoided if risk factors for hepatotoxicity are present (see *NPS News 28: Minimising the risks of using analgesics for musculoskeletal pain*).

## Lumiracoxib is an alternative to other NSAIDs for symptomatic treatment of osteoarthritis

Prescribe lumiracoxib for patients in whom a favourable balance between benefit and harm is expected. The efficacy of lumiracoxib is similar to that of other NSAIDs<sup>4-6</sup>, while risk of adverse events depends on individual renal, cardiovascular and gastrointestinal risk factors (see Box 1). In patients without gastrointestinal risk factors, the difference in adverse effects between lumiracoxib and conventional NSAIDs is small. Response to different NSAIDs varies, so lumiracoxib may also be useful for people who are intolerant of, or have not responded to, other NSAIDs.

Use lumiracoxib for the shortest possible time and periodically evaluate the need for ongoing therapy.<sup>7</sup> Adding an intermittent NSAID (e.g. for symptomatic relief of exacerbations or before painful activities) to regular paracetamol may produce additive benefit and limit the dose of NSAID required.<sup>3</sup>

## COX-2 selective NSAIDs may elevate cardiovascular risk

Lumiracoxib is a COX-2 selective NSAID, and COX-2 selective NSAIDs may increase the risk of serious cardiovascular events relative to placebo or to naproxen. There was an increased rate of cardiovascular events in long-term placebo-controlled trials of rofecoxib (Vioxx) and celecoxib (Celebrex), as well as in a trial of parecoxib combined with valdecoxib for postoperative pain after coronary artery bypass surgery.<sup>8-10</sup> Although there is a biologically plausible mechanism linking the inhibition of the COX-2 enzyme with an increase in thrombotic events<sup>11</sup>, there is not enough evidence from clinical use to draw such conclusions about COX-2 selective NSAIDs as a group. Other trials of COX-2 selective NSAIDs have not had the power to detect important changes in cardiovascular risk.

Evidence for the long-term cardiovascular safety of all NSAIDs is limited. Therefore all NSAIDs should be used with greater caution in people with cardiovascular risk factors.

For further discussion (excluding the evidence on lumiracoxib) see the August 2005 *NPS RADAR* review, Elevated cardiovascular risk with NSAIDs?

## Evidence about the cardiovascular safety of lumiracoxib is limited

The best available comparison of lumiracoxib with conventional NSAIDs in osteoarthritis is the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET).<sup>12-14</sup> TARGET investigated the incidence of upper gastrointestinal ulcer complications as its primary endpoint, as well as the incidence of cardiovascular events such as death, myocardial infarction and stroke.

The trial consisted of two distinct substudies, each involving about 9000 people for 1 year. One substudy compared lumiracoxib with ibuprofen, the other with naproxen; about one-quarter of TARGET participants were receiving low-dose aspirin.

The results of TARGET are inconclusive regarding cardiovascular risk associated with lumiracoxib, as the total number of cardiovascular events in the study was small, resulting in low statistical power. TARGET found no statistically significant differences in the incidence of myocardial infarction, stroke or cardiovascular death between lumiracoxib and either ibuprofen or naproxen. The wide confidence intervals (CIs) indicate that a

### Box 1: Risk factors for gastrointestinal adverse events<sup>18</sup>

- Age  $\geq$  65 years
- History of ulcer
- Concomitant use of anticoagulants or corticosteroids
- Presence of serious comorbidity
- Use of NSAIDs with higher gastrointestinal risk
- Prolonged use of high NSAID doses (which includes the combination of aspirin and another NSAID or of 2 non-aspirin NSAIDs)

clinically significant increase in cardiovascular risk has not been ruled out: the relative risk of a cardiovascular event with lumiracoxib compared with naproxen was 1.46 (95% CI 0.89 to 2.37), while the relative risk for lumiracoxib in the ibuprofen substudy was 0.76 (95% CI 0.41 to 1.40).<sup>13</sup>

The degree of cardiovascular risk associated with using lumiracoxib for longer than 12 months is unknown; rofecoxib toxicity only emerged after 18 months in the APPROVe trial.<sup>9</sup> In a meta-analysis of lumiracoxib clinical trials at all daily doses tested, covering a total exposure to lumiracoxib of about 2000 patient–years, the relative risk of cardiovascular events with lumiracoxib compared with placebo was 1.08 (95% CI 0.41 to 2.86).<sup>15</sup> Again, the CI does not rule out a clinically significant increase in risk and the trials were of short duration, with mean exposure of about 3 months.

### **Lumiracoxib is not recommended for people at high cardiovascular risk**

Lumiracoxib is contraindicated in patients with established ischaemic heart disease (including patients who have recently undergone coronary artery bypass graft surgery), peripheral arterial disease and/or cerebrovascular disease.<sup>7</sup>

Avoid all NSAIDs in people with high background cardiovascular risk. With a high starting point (e.g. absolute 5-year risk of cardiovascular events of 15% or higher), any increase is of particular concern. If an NSAID must be used, prescribe intermittent or short-term therapy to reduce the potential risk, and monitor and manage cardiovascular risk factors. The product information indicates that lumiracoxib should be prescribed with caution for patients with significant cardiovascular risk factors (including diabetes, hypertension, hypercholesterolaemia, congestive heart failure [NYHA II–IV] or smoking).<sup>7</sup> Estimate overall cardiovascular risk using a tool such as the New Zealand Guideline Group's Cardiovascular Risk Calculator ([www.nps.org.au/healthpro](http://www.nps.org.au/healthpro), then choose 'Cardiovascular

risk calculator' from the 'Topics and Resources' menu) when assessing the balance of benefits and harms for lumiracoxib.

### **Low-dose aspirin removes lumiracoxib's gastrointestinal safety advantage**

Patients at increased cardiovascular risk should be considered for low-dose aspirin therapy (see *NPS Prescribing Practice Review 24: Using antithrombotics*). In patients receiving aspirin, lumiracoxib will rarely be the preferred NSAID. When combined with aspirin, lumiracoxib has no gastrointestinal safety advantage over conventional NSAIDs (see next section). Combining any NSAID with aspirin should be done with caution, as the risk of gastrointestinal adverse effects is increased. There is also little evidence that aspirin removes any increased cardiovascular risk associated with NSAIDs.

### **Lumiracoxib caused fewer serious ulcer complications than naproxen or ibuprofen in TARGET**

In TARGET, lumiracoxib caused significantly fewer gastrointestinal perforations, obstructions and bleeds than either naproxen or ibuprofen in patients who did not take aspirin (relative risk 0.21, 95% CI 0.12 to 0.37). As participants in TARGET receiving naproxen or ibuprofen experienced gastrointestinal complications at a rate of about 1% per patient–year, the absolute reduction in risk with lumiracoxib was small: about 120 patients needed to receive lumiracoxib for 1 year rather than ibuprofen or naproxen to avoid one perforation, obstruction or bleed.<sup>14</sup> For patients taking low-dose aspirin, there was no significant reduction in risk (relative risk 0.79, 95% CI 0.40 to 1.55); similarly, the combination of low-dose aspirin and celecoxib was no lower risk than aspirin combined with ibuprofen or diclofenac in the CLASS trial.<sup>16</sup>

Lumiracoxib is not recommended for patients with active peptic ulceration, gastrointestinal bleeding or inflammatory bowel disease.<sup>7</sup> Patients with a history

of gastrointestinal perforations, obstructions or bleeding in the previous 12 months were excluded from TARGET, but for comparison, studies of celecoxib in patients with a previous bleeding ulcer showed a 5% incidence of ulcer recurrence over a 6-month period, despite prior *Helicobacter pylori* elimination.<sup>17</sup>

When possible, all NSAIDs should be avoided in patients at increased gastrointestinal risk (see Box 1 for risk factors), but if the benefits of using an NSAID outweigh the possible harm of causing ulcer complications, lumiracoxib may be preferable to conventional NSAIDs. This is because the absolute reduction in gastrointestinal complications with lumiracoxib compared with conventional NSAIDs is likely to be considerably greater in high-risk patients than in low-risk patients.

## Safety issues

Lumiracoxib has a similar range of adverse effects to those of other COX-2 selective and conventional NSAIDs. Patients taking lumiracoxib have experienced oedema and renal and hepatic adverse effects at a similar rate to those in patients taking conventional NSAIDs. Lumiracoxib caused fewer gastrointestinal complications (perforations, obstructions and bleeds) than conventional NSAIDs in a 1-year clinical trial<sup>14</sup>, but should be used with caution in patients with risk factors for gastrointestinal bleeding. Lumiracoxib may increase the risk of cardiovascular death, myocardial infarction or stroke.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see [www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

### Lumiracoxib elevates liver enzyme concentrations in some patients

As with other NSAIDs, about 1.4% of patients experienced threefold or greater elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with lumiracoxib 200 mg once daily<sup>7</sup>; lumiracoxib 400 mg daily was associated with more frequent elevations and, rarely, cases of hepatitis.<sup>5</sup> Monitor patients who have had an abnormal liver test or who

have other signs of liver dysfunction. Discontinue lumiracoxib if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash).<sup>7</sup>

### As with all NSAIDs, lumiracoxib may cause renal impairment and oedema

Typical NSAID-related adverse effects such as elevated serum creatinine concentration and oedema have been observed in patients receiving lumiracoxib<sup>7</sup>; elevated creatinine concentrations were observed in 3.5% of patients in clinical trials using lumiracoxib 200 mg/day and 400 mg/day.<sup>7</sup>

Lumiracoxib is contraindicated for people with renal impairment with estimated creatinine clearance < 30 mL/min (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m<sup>2</sup>). The elderly and patients with heart failure, existing mild to moderate renal dysfunction, or dehydration or those taking diuretics and ACE inhibitors concomitantly (i.e. the 'triple whammy') are at risk of renal toxicity. Monitor renal function in these patients.

Avoid lumiracoxib, or use only with close monitoring, in patients with fluid retention, hypertension, left ventricular dysfunction or heart failure; discontinue lumiracoxib if there is clinical evidence of deterioration due to oedema.

### Lumiracoxib may potentiate the effects of warfarin

Monitor patients using warfarin, after initiating or altering lumiracoxib treatment. Studies in healthy volunteers showed a mean increase in prothrombin times of about 15% when lumiracoxib was coadministered with warfarin.<sup>7,19</sup>

## Dosing issues

The recommended dosage of lumiracoxib for osteoarthritis is 200 mg once daily. Do not exceed this dosage.<sup>7</sup>

Avoid coadministering lumiracoxib with another NSAID, as using multiple NSAIDs is associated with an increased risk of gastrointestinal complications.<sup>18</sup> Patients who require low-dose aspirin for cardiovascular prevention should receive it; avoid lumiracoxib in these patients if possible (see Place in therapy).

## Information for patients

Suggest or provide the Prexige consumer medicine information (CMI) leaflet when prescribing lumiracoxib.

Advise patients:

- to avoid aspirin and over-the-counter painkillers containing NSAIDs: diclofenac (Voltaren Rapid, Diclac); ibuprofen (Nurofen, Tri-Profen, Herron Blue, Advil, Actiprofen, Compufen, Bugestic, Panafen, Rafen); mefenamic acid (Ponstan); or naproxen (Naprogesic, Alleve, Nurolasts); topical NSAIDs and salicylates may be used, as the level of systemic exposure is very low
- to use paracetamol for minor complaints such as headache and fever
- to try intermittent use as needed during exacerbations or before painful activities.

Discuss the possible adverse effects of lumiracoxib and advise patients to seek prompt medical attention if they experience symptoms suggesting possible gastrointestinal, cardiovascular or renal adverse effects, such as:

- black stools or dark, coffee-coloured vomit
- swollen ankles or feet
- chest pain, irregular heart beat, collapse or fainting.

## References

- Pharmaceutical Benefits Branch. Lumiracoxib public summary document. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-lumiracoxib-nov05> (accessed 15 March 2006).
- Department of Health and Ageing. November 2005 PBAC outcomes: positive recommendations. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-pbacrecnov05-positive> (accessed 23 June 2006).
- Australian Medicines Handbook, 2006.
- Fleischmann R, et al. *Clin Rheumatol* 2006;25:42–53.
- Medicines and healthcare products regulatory agency. UK public assessment report for Prexige 100mg tablets (Lumiracoxib) PL 00101/0677. <http://www.mhra.gov.uk/home/groups/pl-pl/documents/drugsafetymessage/con2022707.pdf> (accessed 3 January 2006).
- Tannenbaum H, et al. *Ann Rheum Dis* 2004;63:1419–26.
- Novartis Pharmaceuticals Australia Pty Ltd. Prexige product information. 29 October 2005.
- Solomon SD, et al. *N Engl J Med* 2005;352:1071–80.
- Bresalier RS, et al. *N Engl J Med* 2005;352:1092–102.
- Nussmeier NA, et al. *N Engl J Med* 2005;352:1081–91.
- Grosser T, et al. *J Clin Invest* 2006;116:4–15.
- Hawkey CJ, et al. *Aliment Pharmacol Ther* 2004;20:51–63.
- Farkouh ME, et al. *Lancet* 2004;364:675–84.
- Schnitzer TJ, et al. *Lancet* 2004;364:665–74.
- Matchaba P, et al. *Clin Ther* 2005;27:1196–214.
- Silverstein FE, et al. *JAMA* 2000;284:1247–55.
- Chan FK, et al. *N Engl J Med* 2002;347:2104–10.
- Wolfe MM, et al. *N Engl J Med* 1999;340:1888–99.
- Novartis Pharmaceuticals UK Ltd. Prexige summary of product characteristics. 2 December 2005. <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=17149> (accessed 23 June 2006).

Date prepared: June 2006

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.

# Alendronate with cholecalciferol (vitamin D<sub>3</sub>) (Fosamax Plus) for osteoporosis

(a-LEN-drun-AYT with KOLL-ee-kal-SIFF-er-ol)

## Summary

- Alendronate with cholecalciferol (vitamin D<sub>3</sub>) contains cholecalciferol 2800 units in a weekly dose, equivalent to 400 units daily. This dose of vitamin D<sub>3</sub> is:
  - inadequate for sole treatment of vitamin D deficiency
  - inadequate for preventing deficiency in high-risk groups
  - the recommended dose to prevent deficiency in the presence of inadequate sunlight exposure in people aged 51–70 years who are not vitamin-D deficient.
- Assess the risk of vitamin D deficiency in people with osteoporosis and a fracture. The major source of vitamin D is sunlight exposure; institutionalised or housebound elderly people have the highest risk of deficiency.
- Vitamin D supplementation does not benefit people with normal vitamin D status — there is no reason to switch such patients from alendronate to the combination product. The combination product could be prescribed in addition to vitamin D<sub>3</sub> 1000-unit supplements to reduce individual cost for patients needing > 3000 units weekly and a bisphosphonate.
- There is no evidence that this combined formulation will reduce the risk of fracture compared with alendronate alone; this was not the basis of PBS listing.
- Vitamin D<sub>3</sub> alone does not reduce fracture risk in people with an existing fracture (secondary prevention). It may have some effect in primary prevention when given with calcium; however, the evidence for this was mostly with a higher vitamin D dose (700–800 units daily).

## PBS listing

### Authority required

Treatment of established osteoporosis in patients with fracture due to minimal trauma.

Patients may only receive one PBS-subsidised anti-resorptive agent at a time.

**Note:** Fosamax Plus provides a supplemental intake of vitamin D. The amount of cholecalciferol (vitamin D<sub>3</sub>) present in Fosamax Plus is not sufficient to use as the sole treatment for correction of vitamin D deficiency.<sup>1</sup>

### Reason for PBS listing

Listing of alendronate with cholecalciferol (Fosamax Plus) was on the basis of similar efficacy to that of alendronate

(Fosamax) for the same cost — that is, cost minimisation. The submission to the Pharmaceutical Benefits Advisory Committee (PBAC) did not claim any greater effectiveness in fracture prevention with the vitamin D component in the combined product.<sup>2</sup>

Although there was no issue of cost, the PBAC was concerned that this product might be inappropriately used to treat vitamin D deficiency. While recognising that patients prescribed bisphosphonates require adequate vitamin D and calcium, the PBAC noted that the target group for this cholecalciferol dosage was not clearly defined.

Currently there is no other vitamin D<sub>3</sub> supplement listed on the PBS (calcitriol is listed but is not recommended for routine treatment of vitamin D deficiency<sup>3</sup>); see Box 1: Types of vitamin D supplement, p.8.

## Place in therapy

Bisphosphonates (such as alendronate or risedronate) are considered first-line therapy for treating patients with osteoporosis and a minimal-trauma fracture.<sup>3</sup>

Adequate calcium and vitamin D are important in maintaining bone health and for the effectiveness of anti-resorptive therapy.<sup>3</sup> Inadequate vitamin D can result in decreased calcium absorption<sup>4</sup>, increased parathyroid hormone concentrations and increased bone turnover.<sup>5</sup>

Whether a vitamin D supplement is needed in addition to alendronate depends on vitamin D status and the risk of deficiency (see inset, Vitamin D and deficiency, p.8).

### Does the patient need a vitamin D supplement and what dose should be used?

Guidelines recommend excluding vitamin D deficiency in elderly people with osteoporotic fractures, and that adequate calcium and vitamin D intake be maintained.<sup>3</sup> People without vitamin D deficiency or obvious risk factors for deficiency are unlikely to benefit from a supplement and there is no reason to switch such patients from alendronate to alendronate with cholecalciferol. Recent consensus guidelines state that 400 units/day is probably enough to prevent deficiency in people who cannot obtain adequate sunlight exposure; however, be aware that people with low vitamin D intake from sunlight and diet may already be vitamin D deficient, and a high-dose supplement would be indicated (see Box 2, p.9).

Deficiency is very common in institutionalised, bed-bound or housebound elderly people (50–80%<sup>6,7</sup>). Other risk factors for vitamin D deficiency include<sup>8</sup>:

- reduced intake or synthesis due to dark skin, or dressing to cover most of the head and body (e.g. veiling)
- malabsorption disorders
- reduced synthesis or enhanced degradation of 25-hydroxyvitamin D (25-OHD) from use of drugs such as rifampicin, phenytoin or multiple anti-epileptic drug therapy, or because of chronic hepatic disorders.

### Do not use alendronate with cholecalciferol as sole treatment for vitamin D deficiency

Alendronate with cholecalciferol contains 2800 units in a once-weekly dose (equivalent to 400 units/day). Treat vitamin D deficiency with cholecalciferol or ergocalciferol at doses of at least 3000–5000 units/day. The maintenance dose to prevent further deficiency is 1000 units/day (see Box 2).<sup>8</sup> Alendronate with cholecalciferol could provide part of this weekly dose along with other 1000-unit supplements, thereby reducing cost to the patient.

### Are there any benefits of supplementing alendronate with vitamin D?

The benefits of vitamin D supplementation in people with adequate serum vitamin D concentrations are unproven.<sup>8,9</sup>

The efficacy trial described in the PBAC submission was an unpublished, randomised double-blind trial comparing alendronate with cholecalciferol to alendronate alone. Crucially, people agreed to limit sunlight exposure for the 15-week trial, and those with vitamin D deficiency (defined in the trial as serum concentration < 22.5 nmol/L) were excluded.<sup>2</sup> Around 21% of participants were classified as vitamin D *insufficient* at baseline (defined as < 37.5 nmol/L), decreasing after treatment to 11% of the combined treatment group and increasing to 32% of the alendronate-only group.

Unfortunately the results of this efficacy trial have limited applicability — they do not apply to people with serum 25-OHD concentrations in the normal or mildly insufficient range who have adequate sunlight exposure. Nor do they apply to people with long-term underexposure to sunlight who may already be deficient and therefore need higher doses. They might apply to people who undergo an unavoidable change in their sunlight exposure, for example, a person having a fall leading to hospitalisation.

Vitamin D insufficiency is usually defined within the range 25–50 nmol/L (see Box 2). From the results of this trial it remains possible that a higher dose of vitamin D<sub>3</sub> will be more effective for this population because:

- 38% of those classified as insufficient at baseline remained so despite 15 weeks' treatment with alendronate and cholecalciferol
- concentrations in the range 37.5–50 nmol/L were not classified as insufficient in this trial, so some people who might be considered insufficient were not included in the efficacy estimates.

**Does vitamin D reduce fracture risk?**

The role of vitamin D in reducing fracture risk remains uncertain. The quantity of vitamin D in alendronate with cholecalciferol is unlikely to reduce risk of fracture, especially in people with a previous fracture.

In secondary prevention (people with an existing fracture), vitamin D<sub>2</sub> or D<sub>3</sub> alone or in combination

with calcium supplementation does not reduce the risk of a further fracture.<sup>10,11</sup>

In primary prevention (mostly postmenopausal women with no previous fracture):

- vitamin D<sub>3</sub> alone does not reduce fracture risk when trials are pooled<sup>11,12</sup> (n = 16,115, relative risk 1.02, 95% confidence interval [CI] 0.92 to 1.13).<sup>11</sup>

**Vitamin D and deficiency**

Vitamin D plays a role in calcium homeostasis, which is regulated by parathyroid hormone.

Cholecalciferol (vitamin D<sub>3</sub>) is obtained from the diet and produced by the action of sunlight on skin. Ergocalciferol (vitamin D<sub>2</sub>) is obtained in the diet from plant sources.

Vitamin D<sub>2</sub> and D<sub>3</sub> are hydroxylated in the liver to hydroxyvitamin D (25-OHD), the main circulating metabolite. 25-OHD is further hydroxylated in the kidneys to 1,25-dihydroxyvitamin D (1,25-OH<sub>2</sub>D), or calcitriol, the active form (Box 1).<sup>5</sup>

**Box 1: Types of vitamin D supplement****Cholecalciferol (D<sub>3</sub>)**

- Available in 1000-unit supplements (over the counter)

**Ergocalciferol (D<sub>2</sub>)**

- Until recently the only vitamin D supplement available in Australia giving 1000 units per dose
- Ergocalciferol may be less effective in increasing 1,25-OH<sub>2</sub>D concentrations than cholecalciferol<sup>23</sup>
- Vitamin D<sub>2</sub> is not reliably detected by assays so monitoring may be more difficult<sup>22</sup>

**Calcitriol**

- The active form of vitamin D — does not require conversion in the kidneys
- Not recommended for vitamin D deficiency, as it has a narrow therapeutic index, a high risk of hypercalcaemia and does not affect serum 25-OHD levels<sup>8,22</sup>

**Vitamin D deficiency: detection, treatment and prevention**

While severe vitamin D deficiency manifests clinically, mild to moderate deficiency may not be obvious. Serum 25-hydroxyvitamin D (25-OHD) levels are the best indicator of vitamin D status and should be maintained at 50 nmol/L or more to prevent and treat osteoporosis in older people.<sup>3</sup> Severity according to serum 25-OHD levels are given in Box 2.<sup>8,24</sup> Note that reference ranges given by laboratories may differ from those shown.

While guidelines for managing vitamin D deficiency are clear<sup>3,22</sup>, the notion of vitamin D insufficiency (or mild vitamin D deficiency) is an emerging concept, and appropriate therapeutic doses are unclear.

**Sources of vitamin D**

Adequate vitamin D intake depends primarily on sun exposure, with a minor dietary contribution; recommendations describe 'adequate intake' rather than 'dietary intake', as for other nutrients. The adequate intakes shown in Box 3 assume no sun exposure.

**Patients who are already vitamin D deficient need a vitamin D dosage greater than the adequate intake in order to replenish depleted stores.**

Note that vitamin D requirements for people with osteoporosis or those taking anti-resorptive therapy have not been adequately determined.

**Sunlight exposure**

- Age, skin colour, season and geographical location (hemisphere and latitude) affect the amount of sunlight exposure required.

- vitamin D<sub>3</sub> with calcium supplementation might have some effect in reducing hip fracture risk (n = 4242, relative risk 0.75, 95% CI 0.62 to 0.91); however, these 3 trials were with vitamin D<sub>3</sub> 700–800 units daily.<sup>11</sup> One trial (the Women’s Health Initiative study<sup>13</sup>) published after this meta-analysis found a small effect on hip fracture in people who adhered to treatment of calcium 1000 mg and vitamin D<sub>3</sub>

400 units daily (hazard ratio 0.71, 95% CI 0.52 to 0.97), but no effect on vertebral or total fractures, or in the primary outcome analysis. About 50% of the women were also taking oestrogen, which is known to decrease fracture risk, making the effect of vitamin D difficult to distinguish.<sup>13</sup>

**Box 2: Serum vitamin D, deficiency and insufficiency<sup>3,22,24</sup>**

Severity of deficiency	Serum 25-OHD range (nmol/L)	Consequences	Treatment
Mild (or insufficiency)	25–50	Mildly elevated serum parathyroid hormone concentrations, increased bone turnover and likely long-term bone loss	Cholecalciferol or ergocalciferol — dose is unclear
Moderate	12.5–25	Secondary hyperparathyroidism, reduced bone density, high bone turnover	Cholecalciferol or ergocalciferol 3000–5000 units daily, for 6–12 weeks. * Continue with 1000 units daily after concentration reaches the normal range
Severe	<12.5	Osteomalacia	

\*There is little risk of vitamin D<sub>3</sub> toxicity in doses of up to 4000 units daily<sup>8</sup>, except in rare cases such as with sarcoidosis.<sup>22</sup>

- In Australia, around 1000 units of cholecalciferol is provided by:
  - 5–9 minutes of sun exposure at 10 am or 2 pm in summer
  - 9–12 minutes in Cairns or Townsville, or 40–47 minutes in Hobart, in winter
  - direct exposure to around 15% of body (hands, arms, face), without sunscreen and not through glass.
- Older people synthesise vitamin D from sunlight more slowly and may require longer or more frequent exposure.
- Advise patients to choose times of low UV activity to avoid skin cancer risk.<sup>8</sup>

For more information on sunlight exposure and vitamin D see *Vitamin D and adult bone health in Australia and New Zealand: a position statement* (Med J Aust 2005;182:281-5).

**Dietary sources of vitamin D**

Vitamin D is obtained in the diet from fatty fish, eggs, liver and fortified foods (some milks and margarines).<sup>9</sup>

- Average dietary intake in Australia is estimated to be around 100 units/day<sup>9</sup>
- It is unlikely that adequate vitamin D concentrations can be obtained from diet alone for most Australians.<sup>8</sup>

**Box 3: Recommended adequate intakes for vitamin D in adults (NHMRC)\*<sup>9</sup>**

Age (years)	Daily intake	
	Units	Micrograms
19–50	200	5
51–70	400	10
71+	600	15

\*Requirements assuming nil intake through sunlight

### Evidence for bisphosphonates and vitamin D

It is not known whether vitamin D further reduces bone loss or fracture risk when added to alendronate.

Adequate vitamin D and calcium intake are considered prerequisites for bisphosphonate therapy<sup>3</sup>, as most efficacy trials were in people with normal calcium and vitamin D status. Alendronate trials usually excluded people with vitamin D deficiencies<sup>14–16</sup> or provided low-dose supplements (e.g. 250 units/day).<sup>17,18</sup> Most provided calcium supplementation.

### Safety issues

Cholecalciferol does not interfere with the absorption of alendronate. The safety profiles of the combined product and alendronate alone appear similar.

Ensure adequate calcium in people with osteoporosis, as low calcium intake may increase vitamin D metabolism and deplete vitamin D.

The most common adverse effects of alendronate are gastrointestinal; see the Fosamax product information or the *Australian Medicines Handbook* for more information on adverse effects and interactions.

Since marketing, new adverse events identified for alendronate include ocular inflammations (uveitis, iritis, scleritis), myalgia and arthralgia and rare instances of jaw osteonecrosis (the latter mostly with high-dose bisphosphonate treatment in patients with cancer, and generally associated with dental work).<sup>19–21</sup>

### Contraindications and precautions

- Alendronate is contraindicated in people with oesophageal disorders that delay emptying and in those not able to stand or sit upright for 30 minutes after administration.<sup>22</sup>
- Vitamin D is contraindicated in hypercalcaemia.<sup>22</sup>
- Alendronate is contraindicated in hypocalcaemia.<sup>21</sup>

- Vitamin D<sub>3</sub> is converted to the active form of vitamin D (1,25-OH<sub>2</sub>D, or calcitriol) in the kidneys; do not use in severe renal impairment.<sup>22</sup>
- Be aware that vitamin D is available in some over-the-counter and complementary medicines.<sup>22</sup>

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see [www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

### Dosing issues

Fosamax Plus is a once-weekly tablet containing alendronate 70 mg and cholecalciferol 2800 units, equivalent to 400 units daily.

Check the dose of vitamin D<sub>3</sub> that the patient requires before prescribing Fosamax Plus. If there is a risk of deficiency consider testing serum 25-OHD levels or prescribe a higher-dose vitamin D<sub>2</sub> or D<sub>3</sub> supplement. Changes in serum 25-OHD levels may take 3–4 months to be detected. See inset, Vitamin D and deficiency.

### Information for patients

Advise patients to take alendronate with cholecalciferol in the morning, with a full glass of water, at least 30 minutes before food or drink; they should remain upright for 30 minutes (sitting, standing or walking around). Antacids, calcium, iron or mineral supplements taken within 30 minutes of alendronate may interfere with absorption.

Suggest or provide the Fosamax Plus consumer medicine information (CMI) leaflet.

Advise patients of the need for adequate sunlight exposure and how to obtain this in a sun-safe manner.

## References

1. Australian Government Department of Health and Ageing. Schedule of Pharmaceutical Benefits, 1 August 2006.
2. Personal communication, Pharmaceutical Benefits Branch, Australian Government Department of Health and Ageing and Merck Sharp and Dohme (Aust) Pty Ltd. May 2006.
3. Therapeutic Guidelines: Endocrinology. Version 3, 2004.
4. Heaney RP, et al. *J Am Coll Nutr* 2003;22:142–6.
5. Sahota O. *Age Ageing* 2000;29:301–4.
6. Zochling J, et al. *Clin Rheumatol* 2005;24:576–82.
7. Flicker L, et al. *J Am Geriatr Soc* 2005;53:1881–8.
8. Working Group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. *Med J Aust* 2005;182:281–5.
9. National Health and Medical Research Council, Australian Government Department of Health and Ageing. Nutrient reference values for Australia and New Zealand. Canberra: Commonwealth of Australia, 2006. <http://www.nhmrc.gov.au/publications/synopses/n35syn.htm> (accessed 15 May 2006).
10. Grant AM, et al. *Lancet* 2005;365:1621–8.
11. Avenell A, et al. *Cochrane Database Syst Rev* 2005:CD000227.
12. Papadimitropoulos E, et al. *Endocr Rev* 2002;23:560–9.
13. Jackson RD, et al. *N Engl J Med* 2006;354:669–83.
14. Pols HA, et al. *Osteoporos Int* 1999;9:461–8.
15. Liberman UA, et al. *N Engl J Med* 1995;333:1437–43.
16. Greenspan SL, et al. *Ann Intern Med* 2002;137:875–83.
17. Black DM, et al. *Lancet* 1996;348:1535–41.
18. Cummings SR, et al. *JAMA* 1998;280:2077–82.
19. Adverse Drug Reactions Advisory Committee. Australian Adverse Drug Reactions Bulletin 2004;23:7–8.
20. Savage R. Alendronate and inflammatory adverse reactions. Information for health professionals. Prescriber update articles. Dunedin: Medsafe New Zealand, 2006.
21. Merck Sharp and Dohme (Australia) Pty Ltd. Fosamax, Fosamax Plus Product Information, 11 June 2006.
22. Australian Medicines Handbook 2006.
23. Armas LA, et al. *J Clin Endocrinol Metab* 2004;89:5387–91.
24. Lips P. *Endocr Rev* 2001;22:477–501.

Date prepared: June 2006.

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.

# Fentanyl patches (Durogesic) for chronic pain

(FENT-a-nil)

## Summary

- Oral morphine is preferred when an opioid is required for severe chronic pain, because of its familiarity, availability and the ease of dose adjustment.
- Reserve fentanyl patches for use in opioid-tolerant patients with chronic pain and established opioid needs who cannot take oral morphine, for example in severe renal impairment. Fentanyl patches might also be useful when oral opioids cannot be used because of vomiting or difficulty swallowing.
- Do not use fentanyl patches in opioid-naïve patients with non-cancer pain because of the potential for serious adverse effects. Fentanyl patches have a delayed onset and prolonged duration of action; adverse opioid effects may be difficult to control.
- Monitor serious adverse effects carefully for 24 hours after removal of the patch, as serum concentrations decline slowly.
- Advise patients to replace patches every 72 hours and no earlier.
- Ensure that patients and carers know about the safe use and disposal of fentanyl patches.

## PBS listing

### Restricted benefit

Chronic severe disabling pain not responding to non-narcotic analgesics.

Restrictions apply for prescribing increased maximum quantities or repeats for opioid analgesics; review by a second medical practitioner is required if opioid therapy extends beyond 1 year.<sup>1</sup>

### Reason for PBS listing

Fentanyl patches can already be prescribed on the Pharmaceutical Benefits Scheme for chronic severe cancer pain. The listing has changed from August 2006 to include chronic non-cancer pain. Listing was approved on a cost-minimisation basis, that is, transdermal fentanyl was no less effective than oral sustained-release morphine, and for similar cost.

The Pharmaceutical Benefits Advisory Committee recommended that transdermal fentanyl should not be initiated in opioid-naïve patients with non-cancer pain, because of a high risk of adverse events.

## Place in therapy

Fentanyl is a strong opioid. The transdermal patch is a long-acting formulation with a delayed onset of effect initially and a prolonged duration of action; plasma concentrations are halved about 17 hours after removal.<sup>2</sup> It is unsuitable for acute pain. Each patch lasts 72 hours. Fentanyl accumulates to form a 'depot' in the skin below the patch, from where it gradually enters the circulation. A matrix 'drug-in-adhesive'\* formulation has replaced the previous gel-reservoir patches, which had problems with leaking<sup>†</sup> and potential for extraction for illicit use.<sup>4</sup>

Oral morphine is generally the first choice when an opioid is required for severe chronic pain, because of its familiarity, availability and range of strengths and formulations that allow greater flexibility in dose titration. Use immediate-release preparations to find the dose that provides effective analgesia with the most acceptable side effects, then switch to a sustained-release preparation to ensure stable, 'round-the-clock' analgesia.<sup>5</sup>

\* Matrix patches were introduced in Australia in 2006 and are expected to replace supplies of reservoir patches by August 2006, when the reservoir patches will be discontinued and withdrawn from the market.

† Two batches of 50 microgram-per-hour patches were recalled in Australia in October 2005 because of reports of leaking.<sup>3</sup>

Reserve fentanyl patches for patients with chronic pain and established opioid needs who are unable to take oral morphine. Fentanyl patches can be useful when morphine cannot be used in severe renal impairment or when the oral route cannot be used because of vomiting or difficulty swallowing.<sup>6,7</sup> Individual response to opioids varies and some patients might experience uncontrollable adverse effects or poor analgesic response to morphine; in such cases fentanyl is one of several alternative opioids that might be considered.<sup>6,7</sup> (See Evidence for fentanyl compared with other opioids, below, and Adverse effects, p.14).

### Risks in opioid-naïve patients

Opioid-naïve patients are vulnerable to potentially fatal opioid effects such as respiratory depression. **Do not use fentanyl patches in opioid-naïve patients with non-cancer pain.**<sup>2,8</sup> The prolonged duration of action of the fentanyl patch means that adverse opioid effects will be difficult to control; its use in opioid-naïve patients is rarely justified. Oral morphine is preferred because of the relative ease of dose adjustments. Although the approved indication and the PBS listing allow use of the fentanyl patch in opioid-naïve patients with cancer pain, it is still best practice to use oral morphine initially to assess how well patients tolerate the opioid and to find the dose that provides stable analgesia. For some opioid-naïve cancer patients the potential harms with the fentanyl patch may be considered acceptable when balanced with expected benefits — if so, start with the lowest-dose patch (12 micrograms per hour) and monitor closely. Wean other analgesics gradually (see Dosing issues, p.15).

For opioid-tolerant patients, see Dosing issues, for equi-analgesic doses of other opioids.

### Always use a stepwise approach to analgesia and pain management

Fentanyl should be prescribed within a stepwise approach to analgesia (as for all opioids<sup>5</sup>):

- use non-drug measures as appropriate, such as exercise, physiotherapy and psychological strategies for pain management
- always start with non-opioids: consider starting opioids when regular dosing of non-opioids (paracetamol, NSAIDs) or weak opioids (codeine, tramadol) is ineffective

- titrate to maximum doses before moving to the next drug
- encourage regular (rather than as-needed) use of analgesics.

Diagnose the type of pain as nociceptive (tissue damage) or neuropathic (nerve damage), as this affects treatment choice<sup>9</sup> (see *Therapeutic Guidelines: Analgesic*<sup>6</sup>).

Discuss and agree on the specific goals of therapy with the patient and document these before embarking on opioid therapy; in non-cancer pain these would include pain relief, functional improvement and quality of life. If goals are not achieved after a reasonable trial, consider stopping the medication.<sup>10,11</sup>

(See NSW Therapeutic Advisory Group guidelines for further details<sup>5</sup>).

Ideally, refer patients with chronic non-cancer pain to a multidisciplinary pain management clinic, especially when<sup>6,7</sup>:

- the diagnosis is uncertain
- there is significant disability, mood change or medication difficulties
- there are multiple issues beyond pain alone
- the patient has a history of substance abuse.

Although waiting lists are often prohibitively long, the change in PBS restrictions means that patients can more easily start opioid treatment while awaiting a pain clinic appointment.

Assess ongoing need for opioids through regular review. PBS authority requirements mean that recent review by a second medical practitioner is needed before opioids can be prescribed for more than 12 months. Although this review does not have to be conducted by a pain specialist, early referral to a pain clinic can ensure appropriate review and also fulfill the PBS requirement.

### Evidence for fentanyl compared with other opioids

There is little good-quality published trial evidence comparing fentanyl with other analgesics in chronic non-cancer pain, and no blinded trials. Most guidelines are based on clinical experience and consensus.<sup>7,11,12</sup>

The available evidence suggests no efficacy advantage over standard opioids. A large, randomised open-label trial (n = 680) in patients with chronic lower back pain found similar effects on pain measured with a visual analogue scale (VAS) when transdermal fentanyl was compared with oral sustained-release morphine.<sup>13</sup> A smaller open-label trial in which patient preference was the primary outcome found small differences in mean VAS ratings, but these were unlikely to be of clinical significance.<sup>14</sup> Some studies have shown that patients prefer fentanyl patches for pain relief over oral morphine, but the lack of blinding means factors other than efficacy cannot be ruled out (e.g. novelty of the delivery mechanism).<sup>14,15</sup>

### Consider the patient's drug and alcohol history

Patients with a history of substance abuse should not be denied effective analgesia for genuine pain. Management is more complex in these patients because:

- previous users of opioids can have high opioid tolerance and may need higher doses for effective analgesia<sup>6</sup>
- concurrent use of alcohol and other central nervous system depressants can have additive effects and place the patient at risk<sup>8</sup>
- there may be a greater risk of dependence in such patients.

Involve pain management or drug and alcohol specialists when possible.

### Renal impairment

Fentanyl can be used in severe renal impairment when other opioids are inappropriate. It is metabolised in the liver and does not have active metabolites.<sup>2</sup>

### Safety issues

Safety issues to consider include the following (see the Durogesic product information for a complete list of interactions and precautions).

- Deaths have occurred with use of fentanyl patches in opioid-naïve patients.<sup>8</sup> Do not use in opioid-naïve patients with non-cancer pain and consider the ratio of benefits to harm before prescribing for cancer pain.

- Elderly patients, in whom there is reduced clearance and a prolonged half-life, may be more sensitive to the effects of fentanyl.
- Do not cut or divide patches.
- Be aware that increased body heat (e.g. fever, humid climate) and direct heat (e.g. from electric blankets, saunas) may increase the rate of absorption.

See the NSW Therapeutic Advisory Group Analgesic Skin Patches alert at [www.nswtag.org.au](http://www.nswtag.org.au).

### Adverse effects

Respiratory depression (hypoventilation) is the most serious potential opioid effect, and accidental overdose may be fatal.<sup>16</sup> Respiratory depression can occur throughout the therapeutic range.<sup>8</sup>

Common opioid adverse effects include nausea, vomiting, constipation, drowsiness and hypotension. Fentanyl may cause less constipation, nausea and vomiting than other opioids, but laxatives are often still required.<sup>2,17</sup> In one large trial, constipation occurred less frequently with fentanyl than with morphine but was still the most frequent adverse effect reported with each drug (52% and 65% of adverse events reported, respectively).<sup>15</sup> Prescribe prophylactic laxatives for all patients taking regular opioid analgesics, including transdermal fentanyl.<sup>2,6</sup>

The patch adhesive may cause erythema or skin irritation.

Monitor serious adverse effects carefully for 24 hours after removal of the patch, as serum concentrations decline slowly.

### Potential for accidental and deliberate misuse

Used patches contain high quantities of residual fentanyl (about 60% of the intended dose<sup>18</sup>). The matrix patches contain higher quantities of fentanyl to achieve the same delivery rate (60–70% more than the reservoir patches).<sup>8,19</sup>

Advise consumers to store and dispose of the patches safely (see Information for patients, below). In institutions, appropriate disposal processes should apply.

Like all opioids, fentanyl carries a risk of dependence and misuse. Addicts may seek out new or used patches. Deaths have occurred with reservoir patches through overdose, application to sites other than skin, and ingestion through various methods. The new matrix

patch formulation patches may eliminate some means of misuse that existed with reservoir patches but the potential for 'creative' misuse remains.

The risk of addiction developing is considered low in most patients using opioids for pain relief, but may be higher in patients with a history of substance abuse.<sup>2</sup> Nonetheless, such patients should not be denied effective analgesia for genuine pain (see Consider the patient's drug and alcohol history, p.14).

### Report adverse events to increase knowledge of fentanyl patches

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see [www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

### Dosing issues

On first application it usually takes 24–72 hours for serum concentrations of fentanyl to reach a peak, so it may not be until the second patch has been applied that a steady-state concentration is reached. Break-through analgesia may be required initially. Wean other analgesics slowly after the first patch.<sup>2</sup>

The patch should be changed every 72 hours.

Fentanyl matrix patches are available in several dosages expressed as the number of micrograms delivered per hour — 12, 25, 50, 75 and 100 micrograms per hour. The older reservoir patches were labelled according to the amount of fentanyl contained in the patch (2.5 mg, 5 mg, 7.5 mg, 10 mg); however, because the matrix patches contain more fentanyl to achieve the same hourly dose, delivery rate rather than total content is now used, to avoid confusion.

If required, titrate the dosage using 12 or 25 microgram-per-hour patches at 72-hour intervals (not less).<sup>8</sup> Estimate needs from doses of break-through analgesia required over several days, but exclude the first patch from this assessment.<sup>6,8</sup>

### Opioid-naïve patients

Ideally all patients should have had recent strong-opioid exposure before starting fentanyl patches. Do not prescribe to opioid-naïve patients with non-cancer pain. If prescribing to opioid-naïve patients with cancer pain, always initiate therapy with the lowest strength patch (12 micrograms per hour). (See Risks in opioid-naïve patients, p.13).

### Opioid-tolerant patients

Dosing should be individualised. People vary in their rate of absorption of fentanyl from the patches<sup>6</sup>, in their ability to tolerate the drug<sup>8</sup> and in analgesic response.

### Dose equivalence in opioid-tolerant patients

When changing patients from another opioid to fentanyl, remember that drug equivalence information is often based on single-dose studies, and **there is substantial individual variation in response**.<sup>2,7</sup> The dose-conversion ranges provided by the manufacturer are only a guide (Tables 1 and 2).<sup>8</sup> Consider using a lower-dose patch initially then titrating upwards.<sup>2</sup>

If the patient has been using an analgesic other than morphine, estimate the morphine-equivalent dose of their previous analgesic using the equi-analgesic doses in Table 1, then use this to estimate their previous 24-hour equivalent oral morphine requirement.

**Table 1: Equipotency of opioid analgesics to oral morphine 30 mg\***

Drug (oral only)	Equi-analgesic dose (mg) to oral morphine 30 mg
Morphine	30 (assuming repeated dosing)
Methadone	20
Oxycodone	30
Codeine	200
Buprenorphine	0.8 (sublingual)

\* This chart shows the dose of oral opioids considered equivalent to 30 mg oral morphine (as a regular dose). For intramuscular equivalents, see the Durogesic product information.<sup>8</sup>

**1. Assess current 24-hour opioid requirement.**

Example: the patient has been taking oxycodone 30 mg tablets, 4 times daily, that is, 120 mg daily.

**2. Convert this to a 24-hour oral morphine equivalent dose.**

Example: the patient has been taking oxycodone 120 mg/day orally. In Table 1, oral oxycodone 30 mg is equivalent to oral morphine 30 mg (assuming repeated dosing). So oxycodone 120 mg/day orally is equivalent to oral morphine 120 mg daily. This is the 24-hour morphine-equivalent dose. Use this value in Table 2.

**3. Based on estimated 24-hour equivalent oral morphine dose, look up the recommended fentanyl patch dose in Table 2 below.**

Example: with an estimated 24-hour-equivalent oral morphine daily dose of 120 mg, the equivalent fentanyl patch is 25 micrograms per hour.

**Table 2: Recommended Durogesic dose based on daily oral morphine dose**

Oral 24-hour morphine (mg/day)	Fentanyl patch (Durogesic) dose (micrograms/hour)
< 135	12–25*
135–224	50
225–314	75
315–404	100

\* The manufacturer advises that the 12 microgram-per-hour patch is considered approximately equivalent to oral morphine 45 mg daily.<sup>18</sup>

**Stopping fentanyl patches**

Drug effects continue after removing the patch as fentanyl concentrations fall slowly, decreasing to 50% after 17 hours.<sup>8</sup> The decline in serum concentrations is slower than with subcutaneous fentanyl because release continues from the depot accumulated in the skin.<sup>2</sup> Withdrawal symptoms may occur; if possible taper slowly to minimise these.

**Information for patients**

Ensure that patients know how to use and dispose of fentanyl patches. Patches should be folded with the sticky sides together, wrapped and disposed of either by returning to the pharmacist, or placing in the garbage well out of reach.

Suggest or provide the Durogesic consumer medicine information (CMI) leaflet. Illustrated leaflets explaining how to use the patches are available to doctors, pharmacists and patients from Janssen-Cilag.

Advise patients to be aware of the following when they use fentanyl patches<sup>2,8,16</sup>:

- Avoid drinking alcohol or using other central nervous system depressants while using a fentanyl patch.
- Apply to a non-hairy part of the upper torso or arms. Hair may be cut before application but not shaved, as this may remove some skin and increase absorption.
- Remove each patch after 72 hours. Date the patch using a marker pen — either the date of application or the date of removal may be used, but be consistent about which is written. Remove the old patch before applying a new one. Apply the new patch to a different site and do not re-use the old site for several days.
- Do not cut or divide the patch or use when damaged.
- Heat may increase the release of drug from the patch, and hot skin may absorb the drug faster, both increasing the risk of adverse effects.
  - Patients should not expose the body to external increases in body temperature, especially on the application site — for example, electric blankets, saunas, heat lamps, wheat packs, hot water bottles, sunbathing or very hot baths.
  - Patients should seek advice from their doctor if they develop a fever.
- Store unused patches and dispose of used patches out of the reach of children. Do not allow children to come into contact with the adhesive, and prevent situations in which the patch may accidentally stick to them (e.g. while sleeping).

## References

1. Department of Health and Ageing. Schedule of Pharmaceutical Benefits, 1 August 2006.
2. Australian Medicines Handbook 2006.
3. Therapeutic Goods Administration. Durogesic 50 microgram/h fentanyl transdermal patches. Medicine recall. Canberra, 2005. <http://www.tga.gov.au/recalls/2005/durogesic.htm> (accessed 27 May 2006).
4. Safety of fentanyl transdermal patches. WHO Drug information 2005; 19. <http://www.who.int/medicines/publications/druginformation/en/> (accessed 9 May 2006).
5. NSW Therapeutic Assessment Group. Prescribing guidelines for primary care clinicians. General principles. Rational use of opioids in chronic or recurrent non-malignant pain. NSW Health, 2002. <http://www.ciap.health.nsw.gov.au/nswtag/publications/guidelines/GeneralPrinciples4=12=02.pdf> (accessed 9 May 2006).
6. Analgesic Writing Group. Therapeutic Guidelines: Analgesic. Version 4. Melbourne: Therapeutic Guidelines Pty Ltd, 2002.
7. Department of Veterans Affairs, Department of Defense (US). VA/DoD. Clinical practice guideline for the management of opioid therapy for chronic pain. Version 1.0. Rockville, 2003.
8. Janssen-Cilag Pty Ltd. Durogesic transdermal system. Product information, 9 Dec 2005.
9. Goucke CR. *Med J Aust* 2003;178:444–7.
10. Graziotti PJ, et al. *Med J Aust* 1997;167:30–4.
11. British Pain Society. Recommendations for the appropriate use of opioids for persistent non-cancer pain, 2004. <http://www.britishpainsociety.org> (accessed 9 May 2006).
12. Chou R. Drug class review on long-acting opioid analgesics. Portland, Oregon: Oregon Evidence-based Practice Centre, 2005.
13. Allan L, et al. *Spine* 2005;30:2484–90.
14. Allan L, et al. *BMJ* 2001;322:1154–8.
15. Ahmedzai S, et al. *J Pain Symptom Manage* 1997;13:254–61.
16. FDA Public Health Advisory. Safety warnings regarding use of fentanyl transdermal skin patches. Rockville, Maryland: Food and Drug Administration, 2005. <http://www.fda.gov/cder/drug/advisory/fentanyl.htm> (accessed 10 May 2006).
17. Clark AJ, et al. *Curr Med Res Opin* 2004;20:1419–28.
18. Janssen-Cilag Pty Ltd. Personal communication. 2006.
19. Janssen-Cilag Pty Ltd. Letter to prescribers. Note important changes to Durogesic: new Durogesic matrix formulation available on the PBS from 1 April 2006. North Ryde: 2006.

Date prepared: June 2006.

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.

# Moxonidine (Physiotens) for hypertension

(mox-ON-i-deen)

## Summary

- Moxonidine is a centrally acting antihypertensive similar to clonidine.
- Moxonidine may be used as add-on therapy to further lower blood pressure if combination therapy with first- and second-line agents is insufficient or unsuitable.
- The effect of moxonidine on cardiovascular morbidity and mortality has not been tested in clinical trials.
- Moxonidine is less likely to cause rebound hypertension than clonidine. Dry mouth and tiredness are the most common adverse effects of moxonidine.
- Do not prescribe moxonidine for people with heart failure of any grade, as it has been associated with increased mortality and adverse events.
- Reduce the dose for people with renal impairment.

## PBS listing

### Restricted benefit

Moxonidine is listed on the Pharmaceutical Benefits Scheme for hypertension when used in combination with other antihypertensive agents.<sup>1</sup>

### Reason for PBS listing

Moxonidine was listed on a cost-minimisation basis compared with clonidine as an add-on therapy for hypertension. The Pharmaceutical Benefits Advisory Committee considered moxonidine to be no worse than clonidine in efficacy and that it appears to be less toxic.

### Place in therapy

Moxonidine is similar to clonidine, but with reduced adverse effects. As with other centrally acting antihypertensives it will be useful for a small proportion of patients who are resistant or intolerant to first- and second-line drugs. While moxonidine lowers blood pressure effectively, there have been no large-scale trials to determine its effect on cardiovascular outcomes. In the UK, moxonidine has been available since 1996 but is not widely used.<sup>2</sup>

### Moxonidine may be used as an add-on therapy if first- and second-line agents are insufficient or unsuitable

Moxonidine is a centrally acting antihypertensive that decreases activation of the sympathetic nervous system.<sup>3</sup> It is similar to clonidine but is selective for imidazoline I<sub>1</sub> receptors over alpha<sub>2</sub>-adrenergic receptors.<sup>4</sup> This selectivity may explain why rebound hypertension appears less common with moxonidine than with clonidine.<sup>4</sup>

Centrally active agents are only recommended if first- and second-line agents fail to control blood pressure or are contraindicated or not tolerated.<sup>5-7</sup> Moxonidine is an alternative to clonidine under these circumstances. A thiazide diuretic is recommended as first-line therapy, except for people with comorbidities that are compelling indications for using another drug class.<sup>5,7</sup> Second-line choices include an ACE inhibitor, a beta blocker or a calcium-channel blocker.<sup>5-7</sup> Combination therapy with up to three agents may be needed to reduce blood pressure sufficiently in some patients.

Moxonidine has been combined with all classes of first- and second-line antihypertensives. Be aware that combining moxonidine with a beta blocker may increase the likelihood of rebound hypertension on withdrawal of moxonidine (see Moxonidine is less likely to cause rebound hypertension than clonidine, opposite).

## The effect of moxonidine on cardiovascular morbidity and mortality has not been tested in clinical trials

Clinical trials of moxonidine have been small scale, of up to 6-months' duration and have not analysed the effect of blood-pressure lowering with moxonidine on cardiovascular morbidity and mortality; in these trials, moxonidine lowered blood pressure as effectively as clonidine and first- and second-line agents.<sup>8–13</sup> The lack of large-scale trials means that UK National Institute for Health and Clinical Excellence (NICE) guidelines do not recommend moxonidine for initial treatment of raised blood pressure.<sup>5</sup>

## Safety issues

Moxonidine causes fewer adverse events than clonidine and in small trials was as well tolerated as first- and second-line antihypertensives. Moxonidine is contraindicated for patients with bradycardia (heart rate < 50 beats/minute), severe bradyarrhythmia, malignant arrhythmia, heart failure or severe renal impairment (see Dosing issues). Moxonidine can potentiate the action of benzodiazepines.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see [www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

## Moxonidine is less likely to cause rebound hypertension than clonidine

No blood pressure rebound effect after sudden discontinuation of moxonidine has been observed in clinical use or in animal models.<sup>3,14,15</sup> Nevertheless, moxonidine should be withdrawn over a period of days rather than stopped abruptly.<sup>3</sup>

The prescribing information states that the likelihood of rebound hypertension when stopping moxonidine may be

increased with patients who are also taking a beta blocker. The beta blocker should be stopped first, then moxonidine withdrawn (as above) a few days later, with blood pressure monitored regularly.<sup>3</sup> The manufacturer has not provided clinical data to support this recommendation.

## Dry mouth and tiredness occur in some patients

Incidence of adverse effects is low, with dry mouth, headache, dizziness and tiredness most common.<sup>3</sup> In 2 small trials the overall incidence of adverse events was less with moxonidine than with clonidine, while blood pressure control was similar.<sup>8,9</sup>

## Do not use moxonidine in people with heart failure of any grade

Moxonidine is contraindicated for people with heart failure, as it appears to worsen outcomes.<sup>3</sup> The MOXCON trial in patients with heart failure was stopped early because of a greater number of deaths among participants who took moxonidine rather than placebo.<sup>16</sup> Hospitalisation for heart failure, and acute myocardial infarction and adverse events were also more frequent in the moxonidine group.<sup>16</sup>

## Dosing issues

Initiate moxonidine at 0.2 mg once daily (in the morning). If blood pressure needs further lowering after 2 weeks, increase to 0.4 mg/day (either as a single morning dose or as 2 divided doses, morning and evening). The dose may be increased to a maximum of 0.6 mg/day after a further 2 weeks, if required. Any single dose should not exceed 0.4 mg.<sup>3</sup>

## Reduce the dose in people with renal impairment

If the estimated creatinine clearance is 30–60 mL/min, each single dose should be no more than 0.2 mg and the daily dose no more than 0.4 mg. Moxonidine is contraindicated if the estimated creatinine clearance is < 30 mL/min.<sup>3</sup>

## Information for patients

Advise patients that moxonidine:

- has dry mouth as its most common side effect
- may cause tiredness or dizziness, and that they should avoid driving or operating machinery if they are affected
- may increase the effects of alcohol or any benzodiazepine-type medicines
- must not be stopped without medical supervision.

For more detailed information about moxonidine, suggest or provide the Physiotens consumer medicine information (CMI).

---

## References

1. Department of Health and Ageing. March 2006 PBAC outcomes: positive recommendations. <http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbacrec-pbacrecmar06-positive> (accessed 27 April 2006).
2. Schachter M, et al. *Int J Clin Pract* 2003;57:479–82.
3. Solvay Pharmaceuticals. Physiotens product information 28 October 2004.
4. Bousquet P, et al. *Ann N Y Acad Sci* 2003;1009:228–33.
5. National Institute for Clinical Excellence. CG34 Management of hypertension in adults in primary care: partial update. 2006. <http://www.nice.org.uk/download.aspx?o=CG034fullguideline> (accessed 7 July 2006).
6. Therapeutic Guidelines: Cardiovascular. Version 4, 2003.
7. Australian Medicines Handbook, 2006.
8. Plänitz V. *J Clin Pharmacol* 1987;27:46–51.
9. Plänitz V. *Eur J Clin Pharmacol* 1984;27:147–52.
10. Vonend O, et al. *J Hypertens* 2003;21:1709–17.
11. Jacob S, et al. *Exp Clin Endocrinol Diabetes* 2004;112:315–22.
12. Prichard BNC, et al. *J Clin Basic Cardiol* 2003;6:49–51.
13. Frei M, et al. *J Cardiovasc Pharmacol* 1994;24[Suppl. 1]:S25–8.
14. Webster J, et al. *J Cardiovasc Pharmacol* 1996;27[Suppl. 3]:S49–54.
15. Rupp H, et al. *Cardiovasc Drugs Ther* 1996;10[Suppl. 1]:251–62.
16. Cohn JN, et al. *Eur J Heart Fail* 2003;5:659–67.

Date prepared: June 2006.

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.

# Adrenaline autoinjector (EpiPen) for acute allergic anaphylaxis

This review of adrenaline autoinjector was first published in December 2003. This update describes the change to the PBS listing to allow prescribing immediately after hospital treatment of allergy-related anaphylaxis with adrenaline, without the previous requirement to first consult a specialist.

## Summary

- A change to the PBS listing means that an EpiPen can be prescribed immediately after hospital treatment for anaphylaxis, without the previous requirement that the prescriber or patient consult a specialist.
- Prescribing an EpiPen is only a small part of managing patients with allergic anaphylaxis.
- Ensure that all patients prescribed an EpiPen have a management plan that includes:
  - referral to a specialist
  - how to avoid triggers
  - education of patients, carers and schools (for children)
  - an anaphylaxis action plan
  - appropriate follow-up and review.
- Even when patients have an EpiPen they often do not use them when needed in an emergency. Train patients to recognise the signs of anaphylaxis and how to use the EpiPen properly.
- EpiPens have a short shelf life; advise patients to check expiry dates regularly.
- See the Australasian Society of Clinical Immunology and Allergy website at [www.allergy.org.au/anaphylaxis](http://www.allergy.org.au/anaphylaxis) for consumer and health professional anaphylaxis resources.

## PBS listing

### Authority required

For emergency treatment of acute allergic reactions with anaphylaxis:

- when risk and clinical need has been assessed by, or in consultation with, a clinical immunologist, allergist, paediatrician or respiratory physician
- after hospital or emergency department discharge for acute allergic anaphylaxis treated by adrenaline.

The authority notes the need for a comprehensive anaphylaxis prevention program and patient action plan. Maximum quantity is one, except for children less than 17 years old, who are eligible for two EpiPens.

## Reason for PBS listing

The listing change (August 2006) allows patients to be prescribed an EpiPen immediately after adrenaline treatment in hospital for an episode of anaphylaxis; this ensures that there is no delay between hospital discharge and EpiPen prescription.

Adrenaline autoinjectors were originally listed on the Pharmaceutical Benefits Scheme in December 2000 on the basis of cost effectiveness compared with placebo. Although the autoinjectors were thought likely to reduce the risk of hospitalisation and death, cost estimates were uncertain because of the unknown size of the 'at risk' population, the potential for under-use in emergencies and the high replacement rate due to short shelf life.

## Place in therapy

Adrenaline is the appropriate first-line emergency treatment for life-threatening anaphylaxis.<sup>1</sup> Early administration of adrenaline can reduce the risk of hospitalisation and death in people at significant risk of anaphylaxis.<sup>2</sup>

Surveys show that only 30–50% of patients who have access to an EpiPen in an anaphylactic episode actually use it.<sup>2,3</sup> Ensure that patients are confident about when and how to use the EpiPen:

- Check that patients and carers know how to use the EpiPen and reinforce this at repeat visits. Rehearsal with an EpiPen trainer (a dummy EpiPen without a needle) can help.
- Make sure that patients and carers have an anaphylaxis action plan that shows when and how to use the EpiPen for an anaphylactic reaction. Advise patients and carers that, if in doubt, it is better to use the EpiPen; it is more harmful to undertreat anaphylaxis than to overtreat a mild allergic reaction.

### Prescribe EpiPen within a comprehensive anaphylaxis management plan

Prescribing an EpiPen is only one part of anaphylaxis management. All patients at risk of allergic anaphylaxis need an overall plan for management of their anaphylaxis (see Box 1). This usually includes:

- referral to an allergy specialist
- identification of triggers
- education on trigger avoidance
- provision of an anaphylaxis action plan
- ongoing follow-up.

If the patient is a child or adolescent it is important that schoolteachers, carers and others who regularly take responsibility for the child are informed about the condition and its management. EpiPen training and anaphylaxis education for teachers and carers is available from First Aid organisations and through some allergy clinics and State Health initiatives. In NSW, *Anaphylaxis Guidelines for schools*<sup>4</sup> is available from NSW Health or through the NSW Department of Education and Training.

#### Box 1: Anaphylaxis management plan (ASCIA)<sup>5</sup>

- Referral to an allergy specialist
- Identification of anaphylactic trigger(s)
- Comprehensive history, clinical examination and appropriate use and interpretation of allergy testing
- Education on the avoidance of trigger(s) (particularly important with food anaphylaxis)
- Provision of an anaphylaxis action plan. This should document:
  - patient name
  - allergic triggers
  - carer contact details
  - symptoms and signs indicating the need to use the EpiPen
  - instructions on how to use the EpiPen

Anaphylaxis action plans with pictorial instructions for EpiPen use can be found at [www.allergy.org.au/anaphylaxis](http://www.allergy.org.au/anaphylaxis)
- Appropriate follow-up, with review by an allergy specialist to:
  - ascertain if the correct trigger(s) have been identified
  - determine whether the allergy persists
  - provide re-education on EpiPen use
  - renew the action plan
  - ensure that the EpiPen has not expired

### Who should be prescribed an EpiPen?

All patients with a history of allergic anaphylactic reaction should have access to an EpiPen. Patients with a history of generalised allergic reactions but without a previous anaphylactic reaction do not usually need an EpiPen. However, a history of generalised allergic reactions and one or more of the risk factors shown in Table 1 warrants consideration of anaphylaxis risk — refer or consult with a specialist allergist or clinical immunologist.

Note the following points.<sup>5</sup>

- Asthma in combination with a history of a generalised allergic reaction increases the risk of anaphylaxis, particularly when there is a food or insect allergy. Most fatal or severe anaphylactic reactions reported have been in people who also had asthma.<sup>6–8</sup> Asthma control is particularly important, as patients with poorly controlled asthma may be less responsive to beta<sub>2</sub> agonists when needed.<sup>7</sup> However, asthma is not a risk factor for anaphylaxis on its own, and adrenaline is not an emergency treatment for asthma.

**Table 1: Guidelines for prescribing EpiPen (ASCIA\*)****ALWAYS RECOMMENDED****HISTORY OF ANAPHYLAXIS****Anaphylaxis**

A rapidly-evolving, generalised multisystem allergic reaction.

Characterised by one or more symptoms or signs of respiratory and/or cardiovascular involvement and involvement of other systems such as the skin and/or gastrointestinal tract.

**Respiratory symptoms**

- Difficult/noisy breathing
- Swelling of tongue
- Swelling/tightness in throat
- Difficulty talking and/or hoarse voice
- Wheeze or persistent cough

**Cardiovascular symptoms**

- Loss of consciousness
- Collapse
- Pale and floppy (in young children)
- Hypotension

**SOMETIMES RECOMMENDED****HISTORY OF A GENERALISED ALLERGIC REACTION AND ONE OR MORE RISK FACTORS****Generalised allergic reaction (non-anaphylactic)**

Characterised by one or more symptoms or signs of skin, with or without gastrointestinal tract involvement and without respiratory and/or cardiovascular involvement.

**Skin symptoms**

- Generalised pruritus
- Urticaria/angioedema
- Erythema

**Gastrointestinal symptoms**

- Abdominal pain
- Vomiting
- Loose stools

**Risk factors**

- Asthma (current or past history)
- Age (children over 5 years, adolescents and young adults)
- Specific allergic triggers:
  - nut/peanut allergy
  - stinging insect allergy in adults (bees, wasps, jumper ants)
- Comorbidity (e.g. ischaemic heart disease)
- Geographical remoteness from emergency medical care

**NOT NORMALLY RECOMMENDED**

- Asthma with no history of anaphylaxis or generalised allergic reactions
- Elevated specific IgE only (positive RAST and/or skin test) without a history of clinical reactions
- Family (rather than personal) history of anaphylaxis or allergy
- Resolved food allergy
- Generalised skin rash (only) to bee stings — in children
- Local reactions to insect stings — in adults and children

\*Abbreviated from ASCIA guidelines for EpiPen prescribing<sup>5</sup>

- Adolescents and young adults are over-represented in allergy-related anaphylaxis deaths, which less commonly involve children under the age of 5 years.<sup>6-8</sup> This could be due to the greater severity of persisting allergies, the less-controlled environment of teenagers, or lower compliance with carrying adrenaline.
- Nut allergy is a common cause of fatal anaphylaxis<sup>8,9</sup>, and exposure can be difficult to avoid. Subsequent episodes may be more severe than the first reaction.

## Safety issues

The potential harms of anaphylaxis almost always outweigh the potential harms of giving adrenaline.<sup>1</sup>

Advise consumers about adrenaline's short shelf life, the need to check and record expiry dates, and to replace their EpiPen before expiry.

EpiPen should be stored below 25°C and protected from light. In hotter areas of Australia where this may be difficult, a portable cooler could be used. Refrigeration is not advised, as the effect on stability is not certain. Regular checking for discolouration can help detect decay of the adrenaline, but this is not an absolute indicator if recommended temperatures are exceeded.

Incorrect administration may result in accidental injury; training should reduce this risk.

## Adverse drug reactions

Few adverse reactions have been reported with the use of EpiPen autoinjectors. Transient pallor, tremor, anxiety, palpitations or other cardiovascular effects, headache and nausea have been experienced.<sup>10-12</sup>

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see [www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

## Dosing issues

The EpiPen autoinjector is available as EpiPen Jr (150 micrograms) and EpiPen (300 micrograms). It should be administered as an intramuscular injection into the anterolateral thigh. Injection into the buttocks is not recommended because of the greater chance of injecting into fat rather than muscle, while injecting into the extremities (hands, feet, face) may stop blood flow to these areas.

### Box 2: EpiPen doses recommended by ASCIA

Weight	EpiPen strength
Children < 10 kg	Not usually recommended
Children 10–20 kg	EpiPen Jr (150 micrograms)
Children and adults > 20 kg	EpiPen (300 micrograms)

Note: The EpiPen product information suggests EpiPen Jr for children 15–30 kg, and EpiPen for those above 30 kg.<sup>11,12</sup> However, the above doses are consistent with routine intramuscular dosing schedules.

## Information for patients

- Advise patients to seek medical treatment immediately in the case of a severe allergic reaction; further adrenaline or other follow-up may be needed even if the EpiPen is used.
- EpiPens tend to be under-used in emergencies, even when one is available.<sup>2</sup> Teach patients how to use EpiPen and reinforce training when needed (poor recall of correct use is common).<sup>2,3</sup> EpiPen trainers are dummy models without a needle, which can be used to practise the correct use of the EpiPen.
- Ensure that all patients have an emergency action plan (see Box 1). Advise that, if in doubt in an emergency, it is safer to use adrenaline than to have an anaphylactic reaction. Action plan proformas are available from the ASCIA website ([www.allergy.org.au/anaphylaxis](http://www.allergy.org.au/anaphylaxis)).

ASCIA has a range of publications about allergies and anaphylaxis for consumers on its website: [www.allergy.org.au/aer/infobulletins/anaphylaxis.htm](http://www.allergy.org.au/aer/infobulletins/anaphylaxis.htm).

## References

1. Australian Medicines Handbook 2006.
2. Gold MS, Sainsbury R. *J Allergy Clin Immunol* 2000;106:171–6.
3. Mullins RJ. *Clin Exp Allergy* 2003;33:1033–40.
4. NSW Health. Anaphylaxis guidelines for schools. Sydney: NSW Department of Health and NSW Department of Education and Training. <http://www.health.nsw.gov.au/pubs/a/pdf/anaphylaxis.pdf> (accessed 26 June 2006).
5. Australasian Society of Clinical Immunology and Allergy (ASCIA). Guidelines for EpiPen prescription. 2004. [http://www.allergy.org.au/anaphylaxis/epipen\\_guidelines.htm](http://www.allergy.org.au/anaphylaxis/epipen_guidelines.htm) (accessed 26 June 2006).
6. Macdougall CF, et al. *Arch Dis Child* 2002;86:236–9.
7. Pumphrey RS. *Clin Exp Allergy* 2000;30:1144–50.
8. Bock SA, et al. *J Allergy Clin Immunol* 2001;107:191–3.
9. Sampson HA et al. *N Engl J Med* 1992;327:380–4.
10. Simons FE, et al. *J Allergy Clin Immunol* 2001;108:1040–4.
11. CSL Limited. EpiPen Jr. Product Information, 11 April 2005.
12. CSL Limited. EpiPen. Product Information, 11 April 2005.

Updated August 2006: PBS listing change to allow prescribing immediately following hospital treatment with adrenaline for anaphylaxis, without the need for patient or prescriber consultation with a clinical immunologist, allergist, paediatrician or respiratory physician.

Updated May 2004: PBS listing change to allow prescribing by or in consultation with respiratory physicians or paediatricians in addition to clinical immunologists or allergists.

First released: 1 December 2003

Date prepared: June 2006.

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.*

### Change of perindopril (Coversyl) salt from erbumine to arginine

The Pharmaceutical Benefits Advisory Committee (PBAC) has approved the change of perindopril salt from erbumine to arginine. The decision was based on bioequivalence of the two formulations of the angiotensin-converting enzyme (ACE) inhibitor. The new salt has improved stability in high humidity but there is no change to the effectiveness of the medicine.

The new formulation is available on the Pharmaceutical Benefits Scheme (PBS) from 1 August. The old erbumine-based formulation will not be removed from the PBS until 1 December, meaning there is a 4-month period when both formulations are available.

While such formulation changes are often inconsequential to how the medicine is used, in this case there are some differences that may cause confusion:

- Tablet strengths have changed slightly
- The 4 mg tablet has changed colour
- Packaging is now a small bottle rather than a blister pack in a box.

The new product has retained its brand name — Coversyl — which may add to the potential for confusion by medicine users not expecting the appearance of the medicine to change.

The table below shows the therapeutically equivalent doses below of perindopril. Note there is **no increase in dose** in moving, for example, from perindopril erbumine 2 mg to perindopril arginine 2.5 mg.

Perindopril arginine (new)		Perindopril erbumine (replaced)
2.5 mg (white, round)	=	2.0 mg (white, round)
5.0 mg (light green, rod-shaped)	=	4.0 mg (white, rod-shaped)
10.0 mg (dark green, round)	=	8.0 mg (dark green, round)

Finally, be aware that the fixed-strength combination tablets of perindopril with the diuretic, indapamide, (Coversyl Plus) will continue to contain the erbumine salt into 2007.

### New vaccine for pertussis, diphtheria and tetanus (Adacel)

Pertussis vaccine acellular with diphtheria and tetanus toxoids (Adacel) has been approved by the PBAC for use under the National Immunisation Program (NIP). The vaccine is restricted to active immunisation in adolescents aged at least 10 years but less than 18 years, as a booster after primary immunisation.

This is the first vaccine to be considered under new arrangements in which advice on funding vaccines has become the function of the PBAC. The NIP, under which the Department of Health and Ageing provides free vaccines to Australians, will replace the Australian Standard Vaccination Schedule.

### Medicines listed on the PBS for Indigenous Australians

On 1 August 2006, thiamine tablets and several topical antifungal preparations were listed on the PBS as authority-required benefits for Aboriginal or Torres Strait Islanders.

The PBAC recommended the listings under the 2004–05 Budget measure 'Improving the capacity of the PBS to meet the needs of Indigenous Australians'.

Thiamine hydrochloride (Betamin) tablets are listed for the prophylaxis of thiamine deficiency. The following antifungal preparations are listed for the treatment of fungal or yeast infection:

- bifonazole 1% cream (Mycospor)
- clotrimazole 1% lotion (Canesten)
- ketoconazole 2% cream and 1% and 2% shampoo (Nizoral)
- miconazole nitrate 2% cream, 2% powder, 2% lotion and 2% tincture (Daktarin)
- nystatin 100 000 units/g cream (Mycostatin).

Medical practitioners should ensure that patients in their practice have the opportunity to identify themselves as an Aboriginal or Torres Strait Islander. For guidance on asking about identification and prescribing medicines under this PBS listing, refer to the Department of Health website at [www.health.gov.au](http://www.health.gov.au) or email [pbs-indigenous@health.gov.au](mailto:pbs-indigenous@health.gov.au).

### New drugs added to palliative care list

The following drugs have been included in the Palliative Care section of the *Schedule of Pharmaceutical Benefits* for patients ineligible to have these medications subsidised via the current PBS listings:

- benzydamine hydrochloride mouth and throat rinse (Difflam)
- lactulose mixture (various brands) and Macrogol 3350 (Movicol) for constipation
- naproxen 125 mg / 5 mL oral suspension (Naprosyn)
- morphine sulfate immediate-release tablets 10 mg, 20 mg (Sevredol)
- morphine sulfate controlled-release tablets 200 mg (MS Contin).

Prescribers are reminded that prescribing opioids must be in accordance with the requirements of State or Territory legislation.

As with all medicines in the palliative care list, quantities for continued supply exceeding one month are allowed only after consultation with a palliative care specialist or service.

For full details of brand names, forms, strengths, and conditions of use, refer to the Schedule.

### Ferrous fumarate 310 mg with folic acid 300 micrograms (Ferro-F-Tab) tablets — unrestricted listing

Ferro-F-Tab was listed on the PBS after the deletion of FGF (ferrous sulfate 250 mg with folic acid 300 micrograms)

on 1 April 2005. The PBAC considered it appropriate that such a product be available for concessional status patients and Indigenous Australians.

Ferro-F-Tab is used to prevent and treat iron and folate deficiency, particularly during pregnancy and in megaloblastic anaemia. Do not start these tablets until vitamin B12 deficiency has been excluded — they do not prevent the neurological damage that B12 deficiency may cause.

### Pseudoephedrine on prescription

From 1 April 2006, pack sizes containing pseudoephedrine 800 mg in liquid form or 720 mg in solid form are now prescription-only. This change is designed to mitigate diversion of pseudoephedrine to the synthesis of methamphetamine by so-called 'pseudo-runners'. Pseudo-runners have previously targeted pharmacies and there have been several recent initiatives for community pharmacies to control pseudoephedrine diversion. For information about these campaigns and pseudoephedrine diversion see the Pharmaceutical Society of Australia web site ([www.psa.org.au/media/FEB2006\\_INPHARMATION\\_SMALL.pdf](http://www.psa.org.au/media/FEB2006_INPHARMATION_SMALL.pdf)).

General practitioners should be aware that, as a result of these changes, pseudo-runners may switch their attention to general practice to gain supply to prescribed quantities of pseudoephedrine.

Pseudoephedrine is indicated for relief of nasal congestion associated with acute or chronic rhinitis. Pooled data support only a moderate benefit from a single dose of oral decongestant in the common cold.<sup>1</sup> Pseudoephedrine is recommended in allergic rhinitis only when severe nasal blockage occurs or when patients need to travel by air.<sup>2</sup>

### References

1. Taverner D, Latte J, Draper M. Nasal decongestants for the common cold. *Cochrane Database Syst Rev* 2004;(3):CD001953.
2. Walls RS, Heddle RJ, Tang MLK, et al. Optimising the management of allergic rhinitis: an Australian perspective. *MJA* 2005;182:28–33.

### Pioglitazone (Actos) and rosiglitazone (Avandia) authority wording changed

The wording of the PBS requirements for pioglitazone and rosiglitazone changed on 1 August 2006. The changes are intended to simplify the listings. The authority requirements for the glitazones have not changed.

As shown in the table at right, both pioglitazone and rosiglitazone are PBS listed (authority required) for dual oral therapy with metformin or a sulfonylurea, and in combination with insulin. Only rosiglitazone is listed for triple oral therapy with metformin and a sulfonylurea.

To be eligible for initiation of a PBS-subsidised glitazone, patients must have a glycosylated haemoglobin (HbA<sub>1c</sub>) level > 7%. The HbA<sub>1c</sub> level, which must have been measured within the 4 months preceding the application, must be provided. A provision has been added to the authority listing to exempt from this requirement patients in whom HbA<sub>1c</sub> testing is likely to be inaccurate (for example, those with thalassaemia

minor). For these patients, results of blood glucose monitoring over 2 weeks, during which more than 20% of results showed a blood glucose concentration above 10 mmol/L, will be accepted.

PBS-listed indications of the glitazones		
Regimen	Pioglitazone (Actos)	Rosiglitazone (Avandia)
Monotherapy	✗	✗
Dual oral therapy (with metformin or a sulfonylurea)	✓	✓
Triple oral therapy (with metformin and a sulfonylurea)	✗	✓
Combination with insulin	✓	✓



## ***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 August 2005 – August 2006

The following *NPS RADAR* reviews are available on our website, [www.npsradar.org.au](http://www.npsradar.org.au). Look for the *NPS RADAR* index in **Quick Links**.

<b>Adrenaline autoinjector</b> (EpiPen) for acute allergic anaphylaxis (updated) . . . . .	August 2006
<b>Alendronate with cholecalciferol</b> (vitamin D <sub>3</sub> ) (Fosamax Plus) for osteoporosis . . . . .	August 2006
<b>Anastrozole</b> (Arimidex) for the treatment of hormone-dependent early breast cancer in postmenopausal women . . . . .	December 2005
<b>Angiotensin II receptor antagonists</b> — unrestricted PBS listing . . . . .	August 2005
<b>Atorvastatin</b> (Lipitor) for the management of lipid disorders . . . . .	December 2005
<b>Buprenorphine transdermal patches</b> (Norspan) for chronic severe pain . . . . .	December 2005
<b>Ciclesonide</b> (Alvesco) inhaler for asthma . . . . .	August 2005
<b>Elevated cardiovascular risk with NSAIDs?</b> . . . . .	August 2005
<b>Eplerenone</b> (Inspra) for use after acute myocardial infarction complicated by heart failure . . . . .	March 2006
<b>Ezetimibe with simvastatin</b> (Vytorin) for dyslipidaemia . . . . .	March 2006
<b>Fenofibrate</b> (Lipidil) for dyslipidaemia (updated) . . . . .	March 2006
<b>Fentanyl patches</b> (Durogesic) for chronic pain . . . . .	August 2006
<b>Lumiracoxib</b> (Prexige) for osteoarthritis . . . . .	August 2006
<b>Metformin/glibenclamide</b> (Glucovance) for type 2 diabetes mellitus . . . . .	December 2005
<b>Methylphenidate</b> (Ritalin) for attention deficit hyperactivity disorder . . . . .	August 2005
<b>Moxonidine</b> (Physiotens) for hypertension . . . . .	August 2006
<b>Rosiglitazone</b> (Avandia) for type 2 diabetes mellitus . . . . .	August 2005

Visit [www.npsradar.org.au](http://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).