

Timely, independent information about new drugs

**Elevated cardiovascular risk with NSAIDs?**

*NPS RADAR* reviews the evidence

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# RADAR

Rational Assessment of Drugs and Research

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

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

Since the withdrawal of rofecoxib (Vioxx) from the market in October last year, the landscape regarding appropriate use of NSAIDs has been changing on almost a weekly basis. The volume of information, coupled with sometimes conflicting advice, has created a level of uncertainty about how NSAIDs can be used safely and effectively in managing pain.

*NPS RADAR* has reviewed the evidence for the gastro-intestinal effects and cardiovascular safety of COX-2 selective and conventional NSAIDs. We present a practical guide to issues prescribers should take into account when considering these drugs, and the evidence that underpins this advice (p.1).

Restrictions on PBS prescribing of angiotensin II receptor antagonists were removed recently on the basis of the available evidence for their safety and effectiveness in treating cardiovascular disease. Removing a restriction and making a medicine a general benefit means the PBS no longer directs the prescriber about the conditions that will be subsidised, so angiotensin II receptor antagonists can now be prescribed on the PBS for all of their TGA-approved indications. Our review (p.8) outlines differences among the approved indications of these agents, compares them to ACE inhibitors, and advises when each might be used.

A new inhaled corticosteroid has been listed on the PBS for managing asthma. Ciclesonide (Alvesco) is a prodrug, converted to its active form in the lungs. Theoretically this could reduce the likelihood of localised adverse effects in the mouth and throat, such as candidiasis and hoarseness. *NPS RADAR*

considers the evidence on adverse effects and compares ciclesonide to other inhaled corticosteroids (p.13).

Methylphenidate (Ritalin) has joined dexamphetamine on the PBS for treating attention deficit hyperactivity disorder (p.15). While methylphenidate has been around for many years, PBS listing for a condition often quoted to occur in about 7% of Australian children and adolescents means prescribing could become more widespread. However, local State or Territory legislation regarding methylphenidate prescribing needs to be observed in addition to the authority required on the PBS.

*NPS RADAR* has revised its review of rosiglitazone several times as new PBS indications have been approved. Most recently, rosiglitazone has been PBS listed for combined use with insulin in people with type 2 diabetes. With two glitazones currently available, both with separate PBS listings, it can be difficult to remember which is approved for use with which antidiabetic medications; we therefore provide a convenient snapshot of the approved PBS listings for both rosiglitazone and pioglitazone (p.20).

You'll find the updated review of rosiglitazone, and all other published reviews, on the *NPS RADAR* website at [www.npsradar.org.au](http://www.npsradar.org.au). Electronic versions of reviews sometimes contain additional information ('web extras') and are made available on the web before the printed publication, which makes registering to receive *NPS RADAR* by email notification a great way to get timely new drug information. Consider registering for this service when you visit the website.

**Timely, independent information about new drugs**

## National Prescribing Service Ltd

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# Elevated cardiovascular risk with NSAIDs?

## Summary

- Elevated cardiovascular risk has been associated with COX-2 selective NSAIDs in some studies. Evidence for the long-term cardiovascular safety of conventional NSAIDs is limited and does not provide strong evidence of a lower risk than for COX-2 selective NSAIDs. Until information is available that distinguishes between them, the most cautious approach is to assume that all NSAIDs carry a similar risk of cardiovascular events.
- All NSAIDs should be used at the lowest effective dose for the shortest possible duration.
- When assessing the need for new or continuing NSAID therapy, carefully weigh the risk of cardiovascular, renal and gastro-intestinal effects against the potential benefits of treatment for each patient.
- All NSAIDs have equivalent efficacy, although there may be interindividual variation in response.
- All NSAIDs have a similar capacity to cause renal impairment, congestive heart failure, hypertension and oedema.
- All NSAIDs can cause serious ulcer complications. Celecoxib appears to have a lower risk of serious ulcer complications than conventional NSAIDs, at least in the short term; the evidence for meloxicam is more limited.

## What action have regulatory authorities taken?

In February 2005, after reviewing the cardiovascular safety of COX-2 selective NSAIDs, the Therapeutic Goods Administration (TGA) advised that their use be restricted (Box 1).<sup>1</sup>

The TGA requested that manufacturers include prominent warnings in the product information for COX-2 selective NSAIDs and proposed to cancel or limit the registration of some of these agents. Overseas regulatory authorities have also warned about the potential for an increased risk of cardiovascular events with COX-2 selective NSAIDs.<sup>2-5</sup> Celecoxib and meloxicam are the only oral COX-2 selective NSAIDs available in Australia.

### Further advice is likely

The TGA is likely to issue further advice on the use of NSAIDs after its review of the cardiovascular and gastro-intestinal safety of conventional NSAIDs is completed,

### Box 1: TGA advice on use of COX-2 selective NSAIDs (14 February 2005)<sup>1</sup>

- COX-2 selective NSAIDs should be prescribed only when other treatments cannot be tolerated or have caused serious adverse effects.
- Celecoxib and meloxicam should not be prescribed for patients at increased risk of cardiovascular events.
- Treatment with celecoxib or meloxicam should be limited to the shortest time needed.
- People taking daily doses greater than celecoxib 200 mg or meloxicam 15 mg should have their treatment reviewed and dose reduced.

which is likely to be by mid-2006.<sup>6</sup> There may also be further changes to the product information for the COX-2 selective NSAIDs. The sponsors of meloxicam have lodged appeals against the TGA's action and have

obtained a Federal Court order to prevent warnings having to appear in the product information for the time being. They have also agreed to provide prescribers and pharmacists with additional precautionary information about the limited cardiovascular safety data available whenever the product information for meloxicam is provided.<sup>7,8</sup> A warning currently appears in the product information for celecoxib, but Pfizer has lodged an appeal with the aim of having it removed.<sup>9</sup>

## What is the evidence of increased cardiovascular risk?

An increased risk of serious cardiovascular events (such as myocardial infarction and stroke) relative to the risk with placebo has been seen in some trials of the COX-2 selective NSAIDs celecoxib, rofecoxib and the combination of valdecoxib and parecoxib. It is not known whether other COX-2 selective NSAIDs (meloxicam, lumiracoxib and etoricoxib) are associated with a similar risk because long-term placebo-controlled trials evaluating their cardiovascular safety are not available.

Evidence for the long-term cardiovascular safety of conventional NSAIDs is limited and does not provide strong evidence for a lower risk than with COX-2 selective NSAIDs. Until there is evidence to distinguish between them, the most cautious approach is to assume that all NSAIDs are associated with a similar risk of cardiovascular events.

### COX-2 selective NSAIDs may elevate cardiovascular risk

Elevated cardiovascular risk was first noted in the VIGOR study in rheumatoid arthritis, in which the incidence of myocardial infarction was four times higher in the rofecoxib 50 mg group than the naproxen group (0.4% vs 0.1%, respectively).<sup>10</sup> There was debate over whether the difference was attributable to a cardioprotective effect of naproxen. When a later trial, APPROVe, found an elevated risk of thrombotic events with rofecoxib 25 mg compared with placebo (1.50 vs 0.78 events per 100 patient-years)<sup>11</sup>, the manufacturer withdrew the drug from the market.

Subsequently, the APC trial of celecoxib for prevention of colon polyps found a significantly elevated risk of cardiovascular events and death in people taking celecoxib 400 mg twice daily compared with placebo

(11.4 vs 3.4 events per 1000 patient-years).<sup>12</sup> People taking celecoxib 200 mg twice daily also had a higher rate of cardiovascular events and death than those on placebo (7.8 vs 3.4 events per 1000 patient-years), but this did not reach statistical significance. Evidence for elevated cardiovascular risk with celecoxib is inconsistent, with two other studies showing no significant difference in the rate of cardiovascular events between subjects taking placebo or celecoxib 400 mg daily.<sup>13</sup> The celecoxib dose most commonly used in Australia, 200 mg/day, has not been used in long-term placebo-controlled trials, so there is currently no evidence to support or refute elevated cardiovascular risk at this dose.

Using parecoxib followed by valdecoxib for post-operative pain after coronary artery bypass surgery has also been found to elevate the risk of cardiovascular events.<sup>14,15</sup> However, a study in general surgery patients failed to find an increased risk of cardiovascular events relative to placebo.<sup>16</sup>

Several observational studies have also indicated an elevated risk of myocardial infarction associated with some COX-2 selective NSAIDs<sup>17–20</sup> although others have found no evidence of significantly elevated risk.<sup>21–23</sup>

Evidence for the effect of dose on the elevated cardiovascular risk possibly associated with COX-2 selective NSAIDs is extremely limited. In the APC trial, the relative risk of cardiovascular death, non-fatal myocardial infarction, stroke or heart failure compared with placebo appeared to increase with dose. Relative risk compared with placebo was 2.3 (95% confidence interval, 0.9 to 5.5) in patients taking celecoxib 400 mg/day and 3.4 (95% CI, 1.4 to 8.5) at a daily dose of 800 mg.<sup>12</sup> Other trials have not evaluated the effects of varying doses but observational studies have found a higher risk with rofecoxib doses above 25 mg than with doses of 25 mg or less.<sup>19–21</sup>

### Evidence for conventional NSAIDs is limited

Studies of the size and duration of those that detected the potential increase in risk relative to placebo for the COX-2 selective NSAIDs have not been conducted for conventional NSAIDs. The highest-quality evidence for the long-term safety of conventional NSAIDs probably comes from the studies in which these were compared with COX-2 selective NSAIDs. VIGOR was the only randomised controlled trial to find a significantly raised risk of myocardial infarction with a COX-2 selective NSAID compared with a conventional NSAID.<sup>10</sup> Other trials do not provide strong evidence of a difference in

cardiovascular risk between COX-2 selective and conventional NSAIDs.<sup>13,24</sup>

A recent trial comparing celecoxib, naproxen and placebo for prevention of Alzheimer's disease found some evidence of an increased risk of cardiovascular events with naproxen.<sup>25</sup> Several observational studies have also indicated a possibly elevated risk of cardiovascular events for people taking conventional NSAIDs compared with people not taking NSAIDs.<sup>17–19</sup>

The United States Food and Drug Administration (FDA) concluded that until further information is available, current data 'are best interpreted as being consistent with a class effect of an increased risk of serious adverse [cardiovascular] events for COX-2 selective and non-selective NSAIDs'.<sup>13</sup> The FDA has requested that US labelling of all prescription NSAIDs include a warning about the potential for increased risk of cardiovascular events and gastro-intestinal adverse effects.<sup>26</sup> The TGA intends to review the cardiovascular safety of conventional NSAIDs before providing further advice.<sup>6</sup>

## Weigh potential benefits against risk of harm for each patient

Carefully compare the risk of harm from using an NSAID with the potential benefits when deciding whether to initiate or continue treatment. This should include considering the value that the patient places on the potential benefits and the risk of harms (Figure 1). When an NSAID is prescribed, ensure that the risks of gastro-intestinal, cardiovascular and renal adverse effects are minimised and that patients understand what to do if they suspect they are experiencing an adverse effect.

### Choosing an NSAID

COX-2 selective NSAIDs have equivalent efficacy and a similar range of adverse effects to those of conventional NSAIDs, so they are not preferred routinely to conventional NSAIDs.

There can be variation in individual response to NSAIDs. If one NSAID is ineffective, it is reasonable to try others, including COX-2 selective NSAIDs.

The most clinically significant difference between COX-2 selective and conventional NSAIDs is likely to be in their propensity to cause serious gastro-intestinal adverse events. However, evidence for a safety advantage for celecoxib or meloxicam over conventional NSAIDs is limited, particularly in the long term. Celecoxib appears to be associated with a reduced risk of ulcer complications,

at least during short-term use; evidence for meloxicam is more limited (see *Risk of serious gastro-intestinal events with available COX-2 selective NSAIDs*).

Using a COX-2 selective NSAID is most justified in people at higher risk of gastro-intestinal adverse effects (Box 3), in whom the absolute reduction in risk of adverse effects will be largest. In the general NSAID-using population, the incidence of serious ulcer complications is low, so the absolute reduction in the risk of complications when using a COX-2 selective NSAID rather than a conventional NSAID is small for most people.

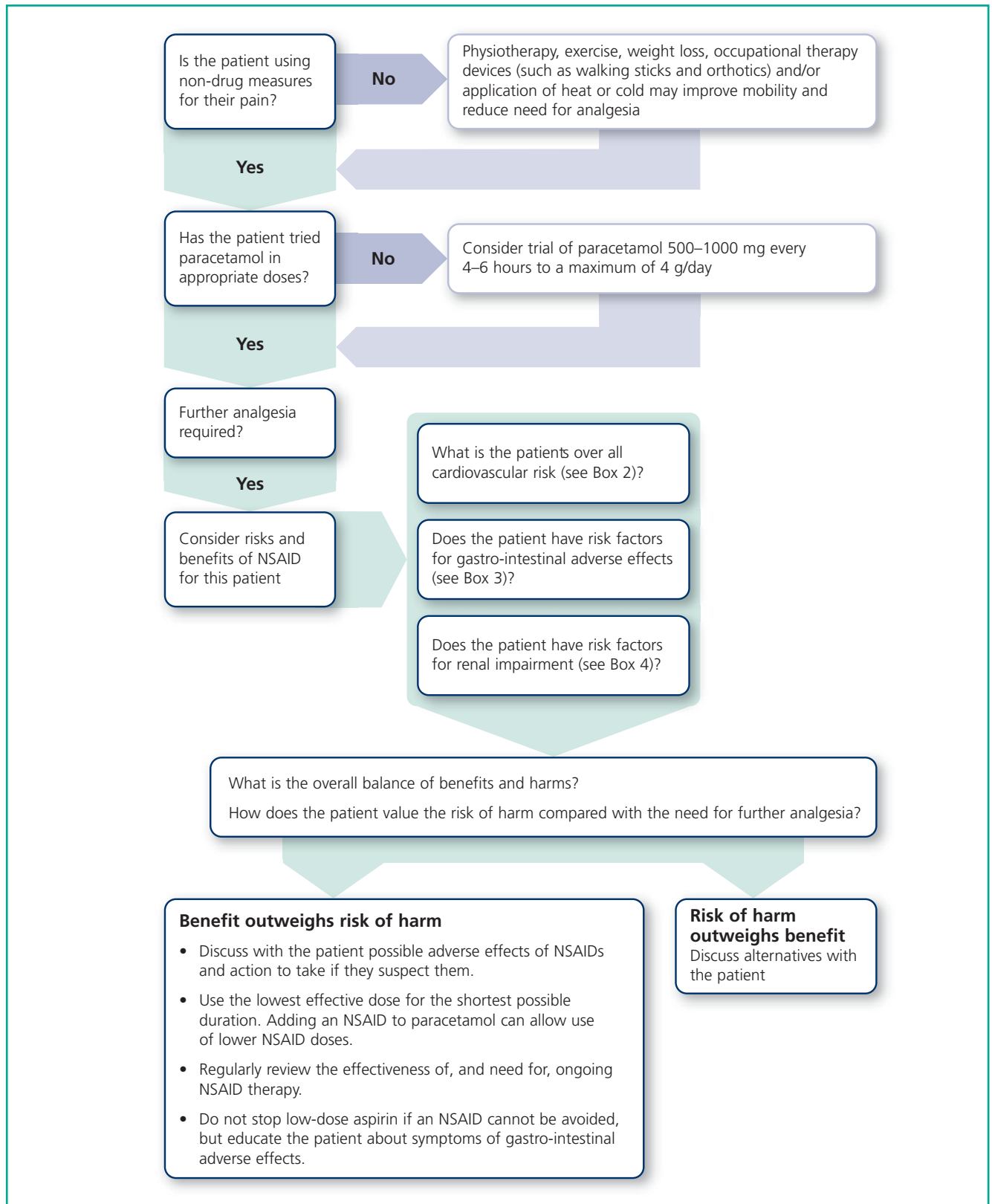
### Risk of serious gastro-intestinal events with available COX-2 selective NSAIDs

Ulcer complications (perforation, outlet obstruction and significant ulcer bleeding) are the most clinically important outcomes on which to assess the gastro-intestinal safety of NSAIDs because these events usually lead to hospitalisation and may be fatal. Some trials use the combined incidence of ulcer complications and symptomatic ulcers (usually defined as uncomplicated gastroduodenal ulcers detected on endoscopy for dyspepsia) as a basis for comparison of gastro-intestinal safety of NSAIDs. However, this is a less clinically important endpoint because many complications occur without a symptomatic ulcer as a precursor, and symptomatic ulcers may not progress to serious complications.<sup>27</sup>

The Pharmaceutical Benefits Advisory Committee has accepted that celecoxib is associated with a lower rate of ulcer complications than conventional NSAIDs for at least the first 3 months of therapy. This conclusion was based on an unpublished pooled analysis of 3-month data from randomised controlled trials.<sup>28,29</sup> It is not clear whether the gastro-intestinal toxicity advantage persists beyond 3 months because reliable long-term data are lacking. A pooled analysis of the only two arthritis trials of at least 6 months' duration found only a marginally statistically significant result in favour of celecoxib. The CLASS study, which was designed to compare the long-term gastro-intestinal toxicity of celecoxib and conventional NSAIDs, failed to find a significantly lower risk of ulcer complications with celecoxib, although definitive conclusions cannot be drawn from this study because it was underpowered to detect a difference between treatment arms and was potentially confounded by a high drop-out rate.<sup>30</sup>

There is no reliable evidence that meloxicam is associated with a lower risk of ulcer complications than other

Figure 1: Pathway for assessing risk of new or continuing NSAID use



**Box 2: Cardiovascular risk**

There is insufficient evidence to establish whether different NSAIDs are associated with varying degrees of cardiovascular risk. Until such information is available, the most cautious approach is to assume that all are associated with the same level of risk. Uncertainty about the relationship of risk to dose or duration of NSAID use underlines the importance of using the lowest effective dose for the shortest possible duration.

**Evaluating the risk**

- 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).

**Minimising the risk**

- Use NSAIDs with greater caution in people at higher cardiovascular risk because they are likely to have larger absolute increases in risk of thrombotic events than those at lower cardiovascular risk. For example, if use of an NSAID were to double the risk of cardiovascular events, the absolute risk for a person with a 5-year risk of cardiovascular events of 2.5% would increase to 5%, whereas for a person with a 5-year risk of 15%, it would increase to 30%.
- Monitor and manage modifiable cardiovascular risk factors.

**Box 3: Gastro-intestinal risk**

COX-2 selective and conventional NSAIDs can cause serious ulcer complications (perforation, obstruction, bleeding)<sup>10,30,34,35</sup> and should be avoided in people at high risk if possible. Celecoxib appears to be associated with a reduced risk of ulcer complications, at least during short-term use; evidence for meloxicam is more limited.

**Evaluating the risk**

Risk factors for gastro-intestinal adverse effects of NSAIDs include<sup>36</sup>:

- age  $\geq$  65 years
- history of ulcer
- concomitant use of anticoagulants or corticosteroids
- presence of serious comorbidity
- use of NSAIDs with higher gastro-intestinal risk
- prolonged use of high NSAID doses (which includes the combination of aspirin and another NSAID or of two non-aspirin NSAIDs).

**Minimising the risk**

- Prefer NSAIDs with a lower risk of serious gastro-intestinal adverse effects (celecoxib, ibuprofen, diclofenac).
- Do not use more than one non-aspirin NSAID concurrently.
- Consider misoprostol or a proton pump inhibitor in combination with a conventional NSAID for people at high risk of gastro-intestinal adverse effects. Misoprostol is the only drug shown to reduce the risk of NSAID-induced ulcer complications. Proton pump inhibitors reduce the risk of gastroduodenal ulcers detected by endoscopy but their effect on the risk of ulcer complications has not been assessed.<sup>37</sup>

**Box 4: Renal risk**

COX-2 selective and conventional NSAIDs have similar risks of renal impairment, congestive heart failure, hypertension and oedema and should be used with caution in people at risk.

**Evaluating the risk**

Risk factors for renal impairment include<sup>38</sup>:

- congestive heart failure
- cirrhosis
- glomerular filtration rate  $\leq$  60 mL/min
- age > 60 years
- use of diuretics, ACE inhibitors, angiotensin II receptor antagonists, cyclosporin or aspirin
- salt-restricted diet

**Minimising the risk**

- If an NSAID is prescribed, assess for symptoms and signs of heart failure, measure weight and blood pressure and assess renal function at baseline, 2–4 weeks after initiation and at regular intervals during treatment.<sup>39</sup>

### Box 5: What about aspirin?

#### Gastro-intestinal adverse effects

Aspirin use increases the risk of gastro-intestinal adverse effects in people taking other NSAIDs. The relative safety of combining a COX-2 selective or conventional NSAID with aspirin is not well evaluated. There is no reliable evidence that, when combined with aspirin, a COX-2 selective NSAID causes fewer ulcer complications than a conventional NSAID. Subgroup analyses in people taking aspirin in trials have found no statistically significant differences in ulcer complication rates between COX-2 selective and conventional NSAIDs.<sup>30,34</sup> Combining any NSAID with aspirin should therefore be done with caution and patients educated about the risks and symptoms of gastro-intestinal adverse effects.

#### Cardiovascular risk

There is little evidence that concomitant aspirin removes the potential excess cardiovascular risk associated with NSAIDs. Cardiovascular risk was elevated to a similar degree in people taking low-dose aspirin at baseline as in the entire trial population in the APPROVe and APC studies.<sup>11,12</sup> In the VIGOR trial, in which aspirin use was not permitted, many of the excess myocardial infarctions that occurred in the rofecoxib group were in patients with an indication for low-dose aspirin therapy<sup>10</sup>, underlining the importance of continuing aspirin therapy when it is indicated.

NSAIDs. A meta-analysis conducted by the UK National Institute for Clinical Excellence showed a lower rate of symptomatic ulcers plus ulcer complications with meloxicam than comparator NSAIDs<sup>31</sup>; however, this analysis relied almost entirely on studies using a daily meloxicam dose of 7.5 mg whereas meloxicam 15 mg tablets are more commonly prescribed in Australia.<sup>32</sup>

Furthermore, the comparator used in many studies in the analysis was piroxicam, which is accepted as having a higher risk of gastro-intestinal adverse effects than ibuprofen, diclofenac or naproxen, which were used as comparators in gastro-intestinal safety studies of other COX-2 selective NSAIDs.<sup>33</sup>

## Information for patients

Discuss with patients of the possible adverse effects of NSAIDs and direct them to seek prompt medical attention if they experience possible gastro-intestinal, 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, or swollen or sore leg veins.

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

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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.

# Angiotensin II receptor antagonists

## — unrestricted PBS listing

### Summary

- The angiotensin II receptor antagonists candesartan, eprosartan, irbesartan and telmisartan are now available on the PBS as unrestricted benefits. This means that PBS-subsidised prescribing of angiotensin II receptor antagonists is no longer limited to hypertension.
- All angiotensin II receptor antagonists are approved by the Therapeutic Goods Administration for use in hypertension, but only some for the additional indications of heart failure and diabetic nephropathy.
- In hypertension an angiotensin II receptor antagonist could be considered in people with coexisting diabetic renal disease or heart failure, particularly when an ACE inhibitor is not tolerated. In uncomplicated hypertension a thiazide would usually be preferred first line; an angiotensin II receptor antagonist could be added when further blood pressure reduction is required.
- In heart failure use an angiotensin II receptor antagonist when an ACE inhibitor is not tolerated.
- The comparative effects of ACE inhibitors and angiotensin II receptor antagonists in diabetic nephropathy are unknown, but ACE inhibitors have been shown to reduce cardiovascular morbidity and mortality in this group whereas angiotensin II receptor antagonists have not.
- Renal impairment, hypotension and angioedema may recur with angiotensin II receptor antagonists in patients with a history of these adverse effects during ACE inhibitor treatment.

### PBS Listing

Angiotensin II antagonists (candesartan, eprosartan, irbesartan and telmisartan) are now listed as unrestricted benefit items. They were previously available as a restricted benefit for hypertension only.

The change means that PBS-subsidised prescribing of angiotensin II receptor antagonists is no longer limited to hypertension. However, indications approved by the Therapeutic Goods Administration (TGA) differ among angiotensin II receptor antagonists. While all are approved for hypertension, only some are approved for heart failure or diabetic renal disease (Table 1). Prescribers are expected to be aware of the TGA-approved indications.

This change does not apply to fixed-dose combination products containing angiotensin II receptor antagonists and diuretics, which are TGA approved for hypertension only.

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended changing the listing on the basis of the available evidence for the safety and effectiveness of angiotensin II receptor antagonists in treating cardiovascular disease, including heart failure, diabetic nephropathy and hypertension.<sup>7</sup>

### Place in therapy

Consider an angiotensin II receptor antagonist:

- as a possible addition to a low-dose thiazide for reducing blood pressure further in uncomplicated hypertension
- when an ACE inhibitor is not tolerated in heart failure
- to slow progression of renal disease associated with type 2 diabetes in people with hypertension.

**Table 1: TGA-approved indications for available angiotensin II receptor antagonists<sup>1-6</sup>**

Generic name (brand name[s])	TGA-approved indications*		
	Hypertension	Heart failure	Diabetic renal disease
Candesartan (Atacand)	✓	✓	✗
Eprosartan (Teveten)	✓	✗	✗
Irbesartan (Avapro, Karvea)	✓	✗	✓
Losartan (Cozaar) <sup>†</sup>	✓	✗	✓
Telmisartan (Micardis)	✓	✗	✗

\*Consult the approved product information for indication details.

<sup>†</sup>Not available on the PBS.

### Consider coexisting conditions in hypertension

Certain coexisting conditions favour the use of particular drug classes in hypertension. Angiotensin II receptor antagonists could be considered in hypertensive people with diabetic renal disease or heart failure (when an ACE inhibitor is not tolerated) because they have evidence of benefit in these patient groups. A table of coexisting conditions favouring the use of particular antihypertensive classes is available on the NPS website ([www.nps.org.au/healthpro](http://www.nps.org.au/healthpro) — go to the 'Topics and Resources' menu, choose 'Products', then 'Health professional tools').

In people with uncomplicated hypertension, consider a low-dose thiazide for initial therapy. Thiazides are at least as effective as other antihypertensives in reducing the risk of cardiovascular events and death.<sup>8</sup>

Most people with hypertension require more than one drug to reach blood pressure target. Add an ACE inhibitor, angiotensin II receptor antagonist or beta-blocker to a low-dose thiazide if further blood pressure reduction is needed.

There is no evidence that angiotensin II receptor antagonists are more effective than other antihypertensives in preventing events such as stroke or myocardial infarction in the general hypertensive population. Some studies in select patient groups have suggested a lower rate of cardiovascular events (but not death) with an angiotensin II receptor antagonist than

with a beta-blocker (in patients with left ventricular hypertrophy)<sup>9</sup> or with a calcium-channel blocker (in patients with previous cerebrovascular events)<sup>10</sup> but these results cannot be generalised to others with hypertension. Other studies have shown no advantage for angiotensin II receptor antagonists over other antihypertensives in reducing the risk of cardiovascular events or death.<sup>11,12</sup>

### Consider in diabetic renal disease

Like ACE inhibitors, irbesartan and losartan slow the progression of diabetic renal disease. A recent meta-analysis found that in patients with hypertension and type 2 diabetes, these two angiotensin II receptor antagonists reduced the risk of a doubling of serum creatinine, end-stage renal disease and progression from microalbuminuria to macroalbuminuria.<sup>13</sup>

Some guidelines suggest that either ACE inhibitors or angiotensin II receptor antagonists be used first line in diabetic renal disease<sup>14,15</sup>, while others recommend ACE inhibitors first because they have a more established evidence base.<sup>16</sup> In the absence of head-to-head trials, the comparative effects of ACE inhibitors and angiotensin II receptor antagonists on the risk of end-stage renal disease or death are unknown. However, note that:

- ACE inhibitors reduce the risk of cardiovascular events and death in people with diabetes, including those with microalbuminuria.<sup>13,17</sup> A survival benefit has not been demonstrated with angiotensin II receptor antagonists.<sup>13</sup>

- ACE inhibitors slow progression from microalbuminuria to overt nephropathy in normotensive patients with diabetes.<sup>18</sup> Evidence of benefit for angiotensin II receptor antagonists in diabetic renal disease is restricted to patients with hypertension.

### Use in heart failure when an ACE inhibitor is not tolerated

All patients with systolic heart failure should receive an ACE inhibitor, if tolerated, whether symptoms are mild, moderate or severe. ACE inhibitors relieve symptoms, reduce hospitalisations and improve survival in patients with heart failure, regardless of functional class.<sup>19</sup> ACE inhibitors should also be used in asymptomatic left ventricular dysfunction because they can prevent progression to heart failure and subsequent hospitalisation.<sup>19</sup>

Use an angiotensin II receptor antagonist when an ACE inhibitor is not tolerated.<sup>19</sup> Candesartan is the only angiotensin II receptor antagonist available that is approved for use in heart failure. In patients with symptomatic heart failure who were unable to tolerate ACE inhibitors, candesartan reduced the absolute risk of cardiovascular death or hospitalisation for heart failure from 40% to 33%.<sup>20</sup>

There is no evidence to support the first-line use of an angiotensin II receptor antagonist in preference to an ACE inhibitor in heart failure. In all studies angiotensin II receptor antagonists were either added to an ACE inhibitor or used when an ACE inhibitor was not tolerated.<sup>20–22</sup>

### Combination ACE inhibitor — angiotensin II receptor antagonist treatment?

The role of combination treatment with an angiotensin II receptor antagonist and an ACE inhibitor in heart failure is uncertain. It has been suggested that this approach be reserved for specialist management.<sup>23</sup>

The Valsartan Heart Failure Trial (Val-HeFT) found that the addition of valsartan to usual therapy (which included an ACE inhibitor in most patients) reduced heart failure hospitalisations but not all-cause mortality. However, in people taking both an ACE inhibitor and a beta-blocker (standard therapy for heart failure), the addition of an angiotensin II receptor antagonist appeared to increase mortality.<sup>21</sup> In the more recent CHARM-Added study, adding candesartan to ACE inhibitor therapy reduced the risk of cardiovascular

death or hospitalisation for heart failure from 42.3% to 37.9%. Unlike Val-HeFT, mortality was not elevated in patients taking beta-blockers.<sup>21</sup> There was a higher rate of discontinuation due to adverse events (mainly hypotension, elevated creatinine concentration or hyperkalaemia) in patients taking candesartan in combination with an ACE inhibitor compared with those using ACE inhibitor alone. Whether the benefit seen justifies the additional risk of adverse events and cost is unclear.

### Exclude other causes of cough before withdrawing an ACE inhibitor

ACE inhibitor-induced cough is typically dry, persistent and worse at night.<sup>24</sup> It tends to occur within months of starting treatment and resolves within a month of stopping treatment.

Discontinuing ACE inhibitor treatment because of cough is rarely required.<sup>24,25</sup> Take care to exclude other causes of cough (such as upper respiratory tract infection, smoking-related disease or gastro-oesophageal reflux) to avoid withdrawing an ACE inhibitor unnecessarily. In patients with heart failure, exclude pulmonary oedema as a cause of new or worsening cough.<sup>25</sup>

Angiotensin II receptor antagonists are less likely to cause cough so they are suitable for people with severe cough (for example, cough that is interfering with sleep) that is probably caused by an ACE inhibitor. Note that when patients with a history of ACE inhibitor-induced cough are randomised to alternative treatment, up to one-third report cough when taking an angiotensin II receptor antagonist or placebo, and a similar proportion do not have recurrence of cough with another ACE inhibitor.<sup>26–29</sup>

### Safety issues

The most common, potentially serious adverse effects of angiotensin II receptor antagonists are renal impairment, hypotension and hyperkalaemia. Angioedema has been reported rarely.

Some adverse effects that lead to discontinuation of an ACE inhibitor may recur during treatment with an angiotensin II receptor antagonist. In the CHARM study, patients who had stopped using an ACE inhibitor because of hypotension, renal impairment or angioedema were more likely to stop using candesartan than placebo for the same reason.<sup>20</sup>

### Use with caution in people with previous ACE inhibitor-induced angioedema

Angioedema may be associated with angiotensin II receptor antagonists and can be life threatening. Angiotensin II receptor antagonist-induced angioedema is rare (although the exact incidence is unknown) and time to onset can vary from less than 24 hours to 3 months or more.<sup>30</sup>

The use of angiotensin II receptor antagonists in people with a history of ACE inhibitor-induced angioedema is a matter of debate. Some consider that angiotensin II receptor antagonists should be contra-indicated in this group because recurrence of angioedema has been reported.<sup>31</sup> In the recent CHARM-Alternative study, angioedema recurred in 3 of 39 patients with ACE inhibitor intolerance due to angioedema or anaphylaxis.<sup>20</sup>

Patients with a history of ACE inhibitor-induced angioedema who subsequently take an angiotensin II receptor antagonist should be closely monitored.

### Consider risk factors for renal impairment, hyperkalaemia and hypotension

Renal impairment, hyperkalaemia and hypotension are possible adverse effects of both angiotensin II receptor antagonist and ACE inhibitor treatment, particularly in patients with heart failure.

Risk factors for renal impairment include renal artery stenosis (either bilateral or of a solitary functioning kidney), severe renal parenchymal disease, hypovolaemia (e.g. associated with diarrhoea or use of high-dose diuretic), old age and concomitant use of NSAIDs (including COX-2 selective NSAIDs).

Hypotension may occur early in treatment with either ACE inhibitors or angiotensin II receptor antagonists. With appropriate management, patients with early symptomatic hypotension can usually tolerate continued treatment with an ACE inhibitor or angiotensin II receptor antagonist.<sup>32</sup>

Hyperkalaemia may occur in people with renal impairment, or those taking potassium-sparing diuretics or potassium supplements. To reduce the risk of these adverse effects:

- avoid ACE inhibitors and angiotensin II receptor antagonists in people with renal artery stenosis

- correct sodium or volume depletion
- stop use of potassium supplements and potassium-sparing diuretics
- check renal function and electrolytes before starting an ACE inhibitor or angiotensin II receptor antagonist, 1–2 weeks after starting and at each dose increment, particularly in patients with risk factors for renal impairment.

### Dosing issues

Dosage recommendations and requirements for adjustment in certain patient groups differ among angiotensin II receptor antagonists. Refer to the *Australian Medicines Handbook* or the individual product information for details.

### Start low and go slow in heart failure

Low starting doses and slow dose titration are required to minimise the risk of hypotension and renal impairment in people with heart failure. Dosage recommendations for heart failure are available only for candesartan because it is the only angiotensin II receptor antagonist approved and available for treatment of heart failure in Australia. A starting dose of 4 mg, doubled every two weeks or longer to reach the target of 32 mg is recommended.<sup>1</sup>

### Information for patients

Advise patients taking an angiotensin II receptor antagonist to:

- stop treatment and seek urgent medical attention if they experience symptoms of:
  - angioedema (swelling of the face, lips, mouth, tongue or throat)
  - renal impairment (dark-coloured urine, passing little or no urine, drowsiness, nausea, vomiting, breathlessness, loss of appetite and weakness)
- return to have their renal function and electrolytes checked 1–2 weeks after starting treatment and at each dose increment.

Suggest or provide the consumer medicine information (CMI) leaflet when you prescribe an angiotensin II receptor antagonist.

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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.

# Ciclesonide (Alvesco) inhaler for asthma

(si-KLESS-oh-nide)

## Summary

- Ciclesonide is an inhaled corticosteroid with efficacy equivalent to that of other inhaled corticosteroids in managing asthma.
- Adverse effects of ciclesonide are the same as for other inhaled corticosteroids.
- Back-titrate to the minimum effective dose of inhaled corticosteroid that maintains asthma control.

## PBS listing

Ciclesonide (Alvesco) inhaler has an unrestricted listing. It is an inhaled corticosteroid used to manage asthma.

## Reason for PBS listing

Ciclesonide was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) on a cost-minimisation basis, with ciclesonide 200 micrograms being equivalent to fluticasone 200 micrograms. Overall, the PBAC accepted that, although there remained considerable doubt about the equi-effective doses across the recommended range for ciclesonide, the trials presented by the company most directly support the 1:1 dose relativity and thus justify giving more benefit of the doubt to the company's request.<sup>1</sup>

## Place in therapy

Ciclesonide is another inhaled corticosteroid for use in the management of asthma. Inhaled corticosteroids are the cornerstone of managing asthma. There is no evidence to suggest that ciclesonide is more effective than existing inhaled corticosteroids. Ciclesonide is administered once daily, which may be more convenient for some patients.

## Ciclesonide is not more effective or safer than other inhaled corticosteroids

Ciclesonide is a prodrug that requires hydrolysis in the lung to form its active metabolite. Because it is not activated until it reaches the lung, ciclesonide may cause fewer adverse effects (particularly local effects in the mouth and throat) than other inhaled corticosteroids.

It is difficult to compare the efficacy and safety of ciclesonide with that of other inhaled corticosteroids, as many studies used doses well in excess of those

currently recommended to manage asthma; for example, ciclesonide 400–1600 micrograms/day was as effective as fluticasone 500–2000 micrograms/day in mild and moderate asthma, with lung function measured by spirometry after provoked bronchospasm.<sup>2–4</sup> (See also *Safety issues*.)

There are no studies published describing ciclesonide's effect on clinical outcomes such as exacerbations, hospitalisations, quality of life or long-term adverse effects.<sup>5</sup>

## Back-titrate to the minimum dose that maintains asthma control

Low and medium doses of inhaled corticosteroids are as effective as higher doses in maintaining asthma control.<sup>6–9</sup> With concurrent use of long-acting beta<sub>2</sub>-agonists (e.g. formoterol, salmeterol) there is now little need to use high doses of inhaled corticosteroids.<sup>10</sup>

After asthma has been well controlled for about 3 months with inhaled corticosteroid, back-titration should be attempted to the minimum effective dose that maintains control. Recommendations vary as to how to back-titrate; one method involves reducing the dose of inhaled corticosteroid by about 25% every 3 months.<sup>10,11</sup>

## Safety issues

Adverse effects of inhaled corticosteroids are dose-related and include local and systemic effects. Local effects include oropharyngeal candidiasis (thrush) and voice hoarseness. Potential systemic effects with long-term use include bruising, cataracts, glaucoma and osteoporosis.<sup>10,11</sup> Data with ciclesonide are limited but there is no reason to expect that the known adverse effects of inhaled corticosteroids will be any different with ciclesonide.

Oropharyngeal effects occurred in clinical trials at a rate higher than that for placebo and comparable to that for budesonide or beclomethasone.<sup>12,13</sup> One study observed higher rates of oral candidiasis (22% vs 2.4%) and hoarseness (7.3% vs 2.4%) with fluticasone than with ciclesonide.<sup>14</sup> However, the dose of fluticasone was high (1000 micrograms/day) and the incidence of oropharyngeal effects seen in this trial is much greater than that commonly reported in adults using inhaled corticosteroids (up to 5%).<sup>13,14</sup>

Compared with fluticasone, ciclesonide consistently demonstrates a significantly lower effect on indices of adrenal suppression such as plasma and urinary cortisol levels<sup>3,4,14</sup>; this might be of benefit in decreasing long-term, systemic adverse effects. However, the doses used in these trials were extremely high (fluticasone 1000–2000 micrograms/day; ciclesonide 400–1600 micrograms/day). Whether ciclesonide exhibits less adrenal suppression than fluticasone at the lower doses typically used for mild to moderate asthma still needs to be determined.

Consult the *Australian Medicines Handbook* or Alvesco product information for more information about adverse effects.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) on-line ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with the *Schedule of Pharmaceutical Benefits*. For information about adverse event reporting, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

## Dosing issues

Back-titrate to the minimum effective inhaled corticosteroid dose that maintains asthma control.

Inhaled corticosteroids have a flat dose–response curve: around 90% of the response is attained with low daily doses equivalent to fluticasone 100–250 micrograms<sup>11,15,16</sup> (equivalent to ciclesonide 100–250 micrograms). In general, dosages above the equivalent of fluticasone 500 micrograms daily are not necessary to maintain control unless asthma is severe.<sup>10,11</sup>

The therapeutic relativity of ciclesonide to other inhaled corticosteroids is not yet established conclusively. Studies comparing ciclesonide to budesonide and fluticasone have used doses likely to be near the flat section of the dose–response curve.<sup>2,4</sup> Therefore, any differences in potency are unlikely to be seen, making equivalent doses difficult to determine.

Ciclesonide is available in two strengths: 80 micrograms per metered dose and 160 micrograms per metered dose. The recommended dose is ciclesonide 80–320 micrograms once daily administered as 1 or 2 puffs.<sup>12</sup>

## Information for patients

For more detailed information about ciclesonide, suggest or provide the Alvesco consumer medicine information (CMI) leaflet.

Patients are advised to rinse their mouth after using inhaled corticosteroids to reduce local effects in the mouth and throat.

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# Methylphenidate (Ritalin) for attention deficit hyperactivity disorder

## Summary

- Diagnosis of attention deficit hyperactivity disorder (ADHD) requires comprehensive information about symptoms and commonly associated conditions. Developmentally inappropriate symptoms with significant impairment should exist in at least two settings (e.g. home, school).
- Methylphenidate and dexamphetamine are the psychostimulant drugs of choice to treat ADHD. They have equal efficacy and a similar range of adverse effects.
- Drug therapy should be combined with educational and psychosocial interventions to support the individual, the family and the school environment.
- Permission from State or Territory departments of health may be required to prescribe psychostimulants, separate to the authority required for PBS prescribing.
- At least annual clinical review is required to measure progress and assess the ongoing need for drug therapy.
- Be alert that the risk of diversion of psychostimulants to people other than for whom they are prescribed can be a problem.

## PBS listing

### Authority required

Methylphenidate 10 mg tablets can be used to treat attention deficit hyperactivity disorder in accordance with State/Territory law.

Requests to the HIC to increase the maximum quantity from 100 tablets with five repeats will be limited to a maximum of 200 tablets with four repeats per authority, to minimise use of methylphenidate at doses above those approved in the product information.<sup>1</sup>

(Note that long-acting Ritalin LA capsules are not PBS listed.)

### Reason for PBS listing

Methylphenidate was recommended for listing by the Pharmaceutical Benefits Advisory Committee (PBAC) on a cost-minimisation basis compared with dexamphetamine sulfate, with methylphenidate hydrochloride 10 mg being equi-effective to dexamphetamine sulfate 5 mg.<sup>2</sup>

## Place in therapy

Psychostimulants should be considered as first-line treatment for attention deficit hyperactivity disorder (ADHD).<sup>3-5</sup> They reduce core symptoms of inattention and hyperactivity/impulsivity.

Methylphenidate and dexamphetamine are considered to have equal efficacy and a similar range of adverse effects.<sup>6-10</sup> Up to 30% of individuals with ADHD will not tolerate or respond to the first psychostimulant used; thorough dose titration and trialling the alternative psychostimulant can improve the response to around 90%.<sup>3,6,11,12</sup>

### Diagnosing ADHD must be comprehensive

Clinical presentation varies greatly between individuals, children and adults, and girls and boys. The core symptoms are inattention (difficulty concentrating), often but not always accompanied by impulsivity and hyperactivity (disorganised, excessive levels of activity).<sup>3,13</sup> Symptoms are developmentally inappropriate and cause functional impairment in daily life. Impairment must be demonstrated in at least two settings (e.g. home, school, clinic, work, socially).<sup>4</sup>

Diagnosing ADHD is not synonymous with a positive response to medication.<sup>5</sup> Additional assessment of co-existing conditions is required as well as details on language, motor skills, emotional vulnerability and school function; family history of similar traits or disorders should be sought.<sup>3,5</sup>

It is advisable that a paediatrician, child psychiatrist or a paediatric neurologist experienced in assessing children with emotional and behavioural problems confirm the diagnosis of ADHD before drug treatment begins.<sup>5,12</sup>

### ADHD in adults

Diagnosis of adult ADHD is controversial; a history of ADHD in childhood is generally agreed to be essential.<sup>5,14,15</sup> There is a wide range of presentations, co-morbidities, severities and outcomes. Psychostimulants are effective and prescribing is increasing<sup>16–18</sup>, with other managements being used concurrently.<sup>15</sup>

### Only authorised medical practitioners can prescribe methylphenidate

General practitioners are normally not permitted to initiate psychostimulant therapy. In some states (e.g. NSW), GPs may continue treatment, particularly in adults. Statutory regulations vary among States and Territories regarding methylphenidate prescribing; for example, in some States prescribers need to apply for permission to prescribe methylphenidate.

Contact the relevant State or Territory department of health (Table 1) for details on how to comply with the provisions of State or Territory law when prescribing methylphenidate.

Methylphenidate is a Schedule 8 controlled drug for which additional prescribing restrictions apply in most States and Territories (e.g. sole drug on prescription, maximum quantity in words and figures, prescriber's details in full and handwritten).

### Always combine medication, school and psychosocial interventions

Cognitive, academic and social benefits vary and are highly individual. There is little evidence that medications for ADHD produce longer-term benefits on a child's academic performance.<sup>11</sup> Similarly, behavioural and psychosocial interventions are not well evaluated: results are inconclusive and require further research.<sup>19</sup> Problems measuring therapy effects in studies relate to the variety of behavioural rating scales available and a lack of

**Table 1: State/Territory authorities to contact about methylphenidate prescribing**

<p><b>Tasmania</b> Pharmaceutical Services Branch</p> <p>Department of Health and Human Services</p> <p>Tel: 03 6233 8011 Fax: 03 6233 3904</p>	<p><b>South Australia</b> Public &amp; Environmental Health Service</p> <p>Department of Human Services</p> <p>Tel: 08 8226 7110 Fax: 08 8226 7102</p>
<p><b>New South Wales</b> Pharmaceutical Services Branch</p> <p>NSW Health</p> <p>Tel: 02 9879 3214 Fax: 02 9859 5165</p>	<p><b>Queensland</b> Pharmaceutical Advisory Services</p> <p>Queensland Health</p> <p>Tel: 07 3234 1167 Fax: 07 3234 0773</p>
<p><b>Western Australia</b> Pharmaceutical Services Branch</p> <p>Department of Health (WA)</p> <p>Tel: 08 9388 4980 Fax: 08 9388 4988</p>	<p><b>Victoria</b> Drugs &amp; Poisons Unit</p> <p>Department of Human Services</p> <p>Tel: 1300 364 545 Fax: 1300 360 830</p>
<p><b>Australian Capital Territory</b> ACT Department of Health &amp; Community Care</p> <p>Pharmaceutical Services, Population Health Division</p> <p>Tel: 02 6207 3974 Fax: 02 6205 0997</p>	<p><b>Northern Territory</b> Poisons &amp; Pharmacy</p> <p>Territory Health Services</p> <p>Tel: 08 8922 7035 Fax: 08 8922 7200</p>

understanding as to how these scales translate into clinically meaningful outcomes.

Despite a lack of firm evidence, it is generally recommended that treatment should be multimodal and consider simultaneous medication use, behaviour management, family knowledge about ADHD as well as counselling and support (e.g. respite, self-help groups), educational management, and specific developmental issues.<sup>4,5,8</sup>

A study of multimodal treatment of children with ADHD found that the effects of methylphenidate alone were equal to those of psychosocial intervention and methylphenidate combined. The combined group, however, achieved an equivalent degree of improvement with a significantly lower dosage of methylphenidate.<sup>20</sup> Striving for combined intervention with a lower dose of medication is preferable to higher-dose medication alone, as the likelihood of adverse drug effects is related to dosage.<sup>4</sup>

Family education about ADHD and guidance in therapy is useful in helping to develop more adaptive problem solving and family interactions. It is often based on working with the family as a group to improve communication and problem-solving skills, develop more effective methods of controlling behaviour and expressing emotion, and encourage new patterns of interaction.<sup>5,21</sup>

Educational interventions are classroom strategies designed to assist in overcoming learning difficulties and to promote consistency of management between home and school. Methods include teacher skills training, role plays and teacher assessment and observation.<sup>5</sup>

Dietary manipulation is not routinely recommended.<sup>4,5</sup> Individual food responses and avoidance may be significant in a minority of patients.

### Review the ongoing need for drug therapy

Treatment and management of patients with ADHD should be reviewed regularly. A review should be conducted at least annually using the same parameters as for the initial diagnosis. Such a review should collect information from multiple sources and specifically evaluate any deterioration following significant interruptions to the medication regimen.<sup>5</sup>

### Safety issues

Psychostimulants can cause a range of troublesome adverse effects, including anorexia and weight loss, abdominal pains, sleep disturbances, headaches, irritability and depressed mood.<sup>3,10,21</sup>

While retarded growth and weight loss are often cited as potential adverse effects of psychostimulants, there does not appear to be any significant long-term effect on height.<sup>4-6,8</sup> Weight and height should nonetheless be monitored.

ADHD is associated with tic disorders. Evidence now suggests stimulant medications do not necessarily precipitate tic disorders: these often wax and wane independent of stimulant use.<sup>22</sup> Treating the ADHD is often the main priority.<sup>3</sup> Nevertheless, caution is advised when using methylphenidate in patients with symptoms or a family history of tics or Tourette's syndrome.<sup>6,8</sup>

The possibility of adolescents sharing medication with peers who do not have ADHD has been reported and is always of concern.

Consult the *Australian Medicines Handbook* or Ritalin product information for more information about adverse effects.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) on-line ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with the *Schedule of Pharmaceutical Benefits*. For information about adverse event reporting, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

### Dosing issues

The response to psychostimulants is commonly rapid and marked.<sup>6</sup> The child, parents, teachers and therapist can each nominate the main target symptoms. It is important to trial one medication at the maximum tolerated dose before declaring no benefit.<sup>3</sup>

Children 6 years and over should start with methylphenidate 5 mg 1–2 times daily, increasing to 3 times daily over 2 weeks.<sup>3</sup> Titrate the dose gradually (e.g. by 5–10 mg weekly up to 2 mg/kg/day) to a maximum dose of 60 mg/day.<sup>8,12,23</sup> Administering psychostimulants three times daily (early morning, mid-to-late morning, and mid-afternoon) sustains treatment effects more steadily at school and benefits homework or evening activities.<sup>4</sup> Methylphenidate should be discontinued if there is no benefit after one month of maximally tolerated treatment.<sup>6,23</sup>

Careful specialist supervision is required in children of preschool age with or without other developmental disabilities (e.g. autism) to optimise dosage.

Methylphenidate is absorbed faster when taken with food; administration should be standardised relative to food to promote a consistent effect.<sup>6</sup> It has been suggested that doses be given with or after food because of the anorectic properties of psychostimulants.<sup>11</sup>

## Information for patients and parents

For more detailed information about methylphenidate, suggest or provide the Ritalin consumer medicine information (CMI) leaflet.

Reassure parents that, although some children show diminished growth rate and weight loss, long-term effects on height are generally not observed.

Reassure parents that psychostimulant therapy does not increase the risk of substance misuse; rather, it reduces the risk of substance misuse later in life.

Alert parents to the potential problem of diversion of psychostimulants to peers and others for whom the therapy is not prescribed. In adolescent patients, reasons why the medicine should not be given to others could be discussed.

Information suitable for patients and their families, including contact details for State-based ADHD support groups, is available from HealthInsite at [www.healthinsite.gov.au](http://www.healthinsite.gov.au).

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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.*

### PBS narcotic authority amended

After consultation with general practice groups and others, the PBAC has clarified its 1 April changes to narcotic analgesic prescribing (see *In Brief* in *NPS RADAR* April 2005).

Changes to the listing of narcotic analgesics were introduced on 1 April 2005 with the objective of increasing access to these drugs in the community for patients with chronic severe pain not associated with malignant neoplasia. Restrictions were aimed at ensuring ongoing clinical need and review. However, concerns were expressed by GP organisations about the authority requirement for GPs to consult a second doctor.

Under the revised authority, GPs do not need to show that they have consulted a second doctor before prescribing increased quantities or repeats of narcotics. However, the drugs cannot be prescribed for more than 12 months unless a pain management review has taken place within the past 3 months.

The authority requirements were changed from 19 April 2005. The note appears in the printed *Schedule of Pharmaceutical Benefits* from 1 August 2005.

The authority allows for increased quantities to be made available for:

- pain associated with proven malignant neoplasia
- other chronic, severe disabling pain that does not respond to non-narcotic analgesics, in one or more of the following scenarios:
  1. the treatment was started in hospital before April 2005 (only applies until April 2006)
  2. the total duration of treatment is less than 12 months
  3. the duration of treatment will exceed 12 months for the first time. In this case doctors will need to supply details that a pain management review has been conducted by a second medical practitioner within the 3 months preceding the request and that clinical need has been confirmed
  4. when a previous authority has been granted for use beyond 12 months for that patient (in accordance with 3 above).

A pain management review only needs to be demonstrated the first time that use will exceed 12 months. From April 2006 patients who have had their treatment initiated in hospital will be subject to the same need for a 12-month review. These requirements only relate to PBS subsidy; State and Territory regulations still apply for the prescribing of narcotics for chronic use.

The drugs covered include:

- hydromorphone
- methadone
- morphine (oral solutions and tablets)
- morphine controlled-release (tablets, capsules and granules — except 200 mg strength)
- oxycodone (tablets, capsules, suppositories and oral solution) and oxycodone controlled-release.

### Quinine now an authority item

Quinine sulfate and quinine bisulfate tablets are now 'authority required' items for malaria only. The PBAC recommended the change to ensure that PBS use is consistent with the approved indications, which have recently been amended to remove the indication relating to muscle cramps. See the *NPS RADAR* review 'Quinine (Quinate, Quinbisul, Quinsul) for muscle cramp' at [www.npsradar.org.au](http://www.npsradar.org.au) for more information.

### Tramadol (Tramal) 100 mg/mL oral drops PBS listed

Tramadol oral drops have been listed as a restricted benefit for pain where aspirin and/or paracetamol alone are inappropriate or have failed. The listing allows for one 10 mL bottle (with dropper device) to be supplied with no repeats. The PBAC recommended the listing of tramadol oral drops on a cost-minimisation basis compared with tramadol 50 mg immediate-release capsules. Tramadol oral drops are also listed on the dental schedule.

Oral drops may be useful for adults who have difficulty swallowing tramadol tablets or capsules. The drops also enable dose titration when increments of less than 50 mg are required. A dose of 20 drops is equivalent to one 50 mg immediate-release capsule. The dosing

recommendations are the same as for tramadol immediate-release capsules. As this is a concentrated formulation (100 mg/mL), care is advised when administering.

Tramadol oral drops are not a paediatric formulation. Tramadol is not approved for use in children under 12 years of age. The bottle has a 'push down and turn' safety cap to help prevent accidental ingestion by small children.

### Change to current PBS eligibility requirements for prescribing bDMARDs for severe rheumatoid arthritis

As of 1 June 2005, the need to be rheumatoid factor positive was removed from the restrictions of the four biological disease-modifying anti-rheumatic drugs (bDMARDs) — adalimumab (Humira), anakinra (Kineret), etanercept (Enbrel) and infliximab (Remicade) — available through the PBS to treat severe active rheumatoid arthritis.

Previously, it had been a requirement of PBS-subsidised prescribing of bDMARDs that the patient was rheumatoid factor positive. This was because initial evidence suggested that rheumatoid factor status was important as a treatment effect modifier: patients who were rheumatoid factor positive appeared to have a significantly greater response to bDMARDs.

As evidence accumulated with these agents, it became apparent that rheumatoid factor status was perhaps not as important in modifying response as first thought. The PBAC noted that there is suggestive evidence of a weak modifying of treatment effect by rheumatoid factor status, such that being rheumatoid factor negative may result in inferior response rates compared with being rheumatoid factor positive. However, as the level of response required to receive repeat treatment with a bDMARD would be the same for rheumatoid factor negative and rheumatoid factor positive patients, the lower response rate became less of an issue.<sup>1</sup>

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### New strength of metformin and glibenclamide (Glucovance) combination tablets PBS listed

The combination tablet of metformin and glibenclamide (Glucovance) was listed on the PBS in April 2005 and was discussed in an *NPS RADAR* review at that time.

A new strength of metformin and glibenclamide tablets (250 mg/1.25 mg) was listed on the PBS from 1 August 2005. This lower-strength tablet is recommended for initial dosing in the elderly. It may also be useful in patients who experience hypoglycaemia during dose titration with the higher-strength tablets (500 mg/2.5 mg and 500 mg/5 mg). Closely monitor blood glucose levels when prescribing any strength of Glucovance and ensure that patients and their carers are aware of the signs and symptoms of hypoglycaemia (e.g. sweating, palpitations).

### The 'glitazones' — PBS-listed indications

With the new PBS listing for rosiglitazone in combination with insulin (see the updated review at [www.npsradar.org.au](http://www.npsradar.org.au)), the only difference in the PBS-listed indications of the two thiazolidinediones is that rosiglitazone, but not pioglitazone, is listed for use in combination with metformin and a sulfonylurea (see table).

#### PBS-listed indications for thiazolidinediones

	Pioglitazone (Actos)	Rosiglitazone (Avandia)
Monotherapy	✗	✗
Dual oral therapy (with metformin or a sulfonylurea)	✓	✓
Triple oral therapy (with metformin and a sulfonylurea)	✗	✓
Combination with insulin	✓	✓



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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.

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<b>Angiotensin II receptor antagonists</b> — unrestricted PBS listing	August 2005
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<b>Sertraline</b> (Zoloft), fluoxetine (Lovan, Prozac) for premenstrual dysphoric disorder	December 2004

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