

## In Brief

*A digest of news items about NPS RADAR, new drugs and changes to PBS listings.*

### **Clopidogrel (Iscover, Plavix) PBS listing extended to include acute coronary syndrome (ACS) in combination with aspirin**

Clopidogrel and aspirin can now be prescribed in combination for acute coronary syndrome (ACS) as an authority (streamlined) item on the Pharmaceutical Benefits Scheme (PBS). The extended listing, which came into effect on 1 February 2009, includes the treatment of myocardial infarction (MI) or unstable angina to prevent early and long-term atherothrombotic events.

The Pharmaceutical Benefits Advisory Committee (PBAC) agreed that clopidogrel plus aspirin is more effective in ACS than aspirin therapy alone, but is associated with a higher risk of bleeding.<sup>1</sup> In clinical trials of patients with ACS, the benefit of combined therapy exceeded risk.<sup>2,3</sup> In summary:

- there is a higher risk of bleeding with combined therapy
- for about every 3 serious cardiovascular events prevented in ACS patients without ST-segment-elevation, 1 patient will experience a major bleed requiring transfusion<sup>2</sup>
- there is a possibility of rebound cardiac effects after stopping clopidogrel
- the optimal duration of combined therapy is unknown, and should be determined on an individual basis.

#### **Place in therapy**

Consider clopidogrel in combination with aspirin for patients with ACS (unstable angina, non-ST-segment-elevation MI or ST-segment-elevation MI).<sup>4,5</sup> If possible, clopidogrel should be discontinued 5 days before coronary artery bypass surgery, and avoided in patients likely to undergo emergency coronary artery bypass surgery.<sup>6</sup>

#### **Clopidogrel prevents thrombotic events and deaths**

The extended listing was informed by two randomised, double-blind clinical trials. One study (CLARITY) enrolled patients with ST-segment-elevation MI<sup>3</sup> and the other (CURE) enrolled patients with ACS without ST-segment-elevation.<sup>2</sup>

In the CLARITY study, in which 3491 patients were followed for 30 days, there was an absolute risk reduction of 6.7% in the primary outcome (occluded infarct-related artery on angiography, death or recurrent MI before angiography) in patients receiving clopidogrel and aspirin, compared with those receiving aspirin alone.<sup>3</sup>

In the CURE study, 12562 patients were randomised to receive clopidogrel and aspirin, or aspirin alone, for 3–12 months (mean treatment duration 9 months). The absolute risk of death from cardiovascular causes, non-fatal MI or stroke was reduced by 2.1% in patients receiving clopidogrel and aspirin, compared with those receiving aspirin alone.<sup>2</sup>

#### **Optimal duration of clopidogrel therapy is unknown**

The optimal duration of clopidogrel therapy in ACS is unknown. It will depend on individual medical circumstances and may be influenced by the category of ACS index event, type of stent implanted (if relevant), the absolute risk of further ischaemic events and the risk of bleeding (see Potential risk for major bleeding). The decision to discontinue antiplatelet therapy after ACS or stent implantation, including discontinuation for surgery, should be made in consultation with the patient's cardiologist.<sup>7,8</sup> After withdrawing clopidogrel, low-dose aspirin (unless contraindicated) should be continued indefinitely.<sup>6</sup>

Current Australian guidelines recommend clopidogrel 75 mg daily in addition to aspirin in the medical management of high-risk non-ST-segment elevation ACS (duration of therapy not specified).<sup>6</sup> Patients with ST-segment-elevation MI should take clopidogrel (75 mg daily) for at least 1 month after fibrinolytic therapy, and for up to 12 months after stent implantation\*.<sup>6</sup> The optimal duration of clopidogrel therapy may be greater in patients treated with a drug-eluting stent, compared with those treated with a bare metal stent.<sup>7,9</sup>

Formal studies assessing extended or indefinite periods of clopidogrel therapy, tapering of clopidogrel therapy, or bridging of clopidogrel cessation to transient high-dose aspirin have not been conducted in patients with ACS.

\* Depending on the type of stent and circumstances of implantation.

### Potential risk for major bleeding

Combined therapy is associated with a small absolute increased risk of bleeding. However, in clinical trials the benefit of clopidogrel and aspirin in patients with ACS with or without ST-segment-elevation outweighed the risk of major bleeding.

Data from the CURE study indicate that for about every 3 serious cardiovascular events prevented in ACS patients without ST-segment-elevation, 1 patient will experience a major bleed requiring transfusion.<sup>2</sup> The risk of any major bleeding\* in patients receiving clopidogrel and aspirin therapy was small, but it was higher than that of patients receiving aspirin alone at 12 months.<sup>2</sup>

In the CLARITY study, the incidence of major bleeding was not significantly greater in patients receiving clopidogrel and aspirin than those receiving aspirin alone during the day after angiography or at 30 days.<sup>3</sup>

The CURE trial excluded patients at high risk for severe heart failure or bleeding (not otherwise specified), and those taking oral anticoagulants. Therefore, use clopidogrel with caution in this population and inform patients that bleeding may take longer than usual to stop while taking clopidogrel. Monitor patients for signs of bleeding, particularly during the first few weeks of treatment and after invasive procedures or surgery. Advise patients or carers to immediately report unusual bleeding or bruising, abnormal nose bleeds or bloody or black bowel motions.<sup>4,5</sup>

### Risk of rebound cardiovascular events on cessation

A retrospective study found an increased risk of death or acute MI (rebound effects) after stopping clopidogrel.<sup>10</sup> The absolute increase in risk was small. This effect has not been confirmed in a randomised controlled trial, and it is not known how the increased risk after stopping clopidogrel compares to that of patients who have never received clopidogrel.

The cohort study included 3137 patients who received percutaneous coronary intervention (PCI) or medical treatment (mean duration of clopidogrel 302 and 278 days, respectively) for ACS. The risk of death or acute MI was greatest during the first 3 months after

stopping clopidogrel and was nearly twice that found in the following 3 months. However, the absolute risk in the first 3 months after stopping was small; 0.57 deaths or acute MIs per 1000 patient days of follow-up in PCI-treated patients and 1.31 in medically treated patients. The rate of events in medically treated patients during the first 3 months after stopping clopidogrel treatment was higher than that for the first 3 months of clopidogrel treatment, and the subsequent 9 months of treatment.

Any decision to discontinue clopidogrel therapy should be made in consultation with the patient's cardiologist and include an assessment of the individual risk of recurrent vascular events against the risk of major bleeding.

### Reason for PBS listing

The PBAC recommended a streamlined authority listing of clopidogrel for the treatment of ACS in combination with aspirin. The decision was reached on the basis of acceptable cost-effectiveness compared with aspirin alone.

### Information for patients and carers

Advise patients and carers of the following:

- clopidogrel and aspirin can be used together for heart attack or unstable angina
- both medicines can cause bleeding, and the risk of major bleeding is increased when they are used together
- immediately report unusual bleeding or bruising, abnormal nose bleeds or bloody or black bowel motions
- aspirin must be continued, even if clopidogrel is stopped.

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\* Major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating transfusion of at least 2 units of blood.

## Ziprasidone (Zeldox): another atypical antipsychotic listed for acute mania in bipolar disorder

Ziprasidone (Zeldox) was PBS listed on 1 April 2009 for treating acute mania or mixed episodes in people with bipolar I disorder. The streamlined authority listing allows ziprasidone monotherapy for up to 6 months. Ziprasidone was previously PBS listed for schizophrenia only.

Mood stabilisers (e.g. lithium) remain the mainstay for treatment and maintenance (prophylaxis) of mania in bipolar disorder. Atypical antipsychotics are sometimes recommended, particularly for severe episodes of acute mania, because of their faster onset of effect (1–2 days).<sup>1–4</sup>

### Approved indications and PBS listings differ between antipsychotics

**Acute mania:** quetiapine (Seroquel) and risperidone (Risperdal) are the other atypical antipsychotics PBS listed for acute mania.<sup>5</sup> Of these, only risperidone can currently be prescribed on the PBS as adjunctive therapy (see Table 1).

**Mixed episodes:** ziprasidone is PBS-listed for use in mixed episodes of bipolar 1 disorder.

**Maintenance therapy:** olanzapine is currently the only atypical antipsychotic with a PBS listing for maintenance therapy in bipolar disorder.

**Table 1. Indications and PBS listings for atypical antipsychotic drugs in bipolar I disorder**

Drug	ACUTE MANIA		MAINTENANCE	
	TGA approved	PBS listed	TGA approved	PBS listed
Olanzapine (Zyprexa)	Yes (monotherapy or adjunctive therapy)		Yes	Yes
Quetiapine (Seroquel)	Yes (monotherapy or adjunctive therapy)	Yes (monotherapy)	Yes (adjunctive therapy only)	
Risperidone (Risperdal)	Yes	Yes (adjunctive therapy only)		
Ziprasidone (Zeldox)	Yes (monotherapy), mixed episodes	Yes (monotherapy)		

### Evidence of efficacy in acute mania, not for maintenance therapy

The evidence for ziprasidone for reducing symptoms of acute mania comes from 2 short (3 week) blinded randomised controlled trials.<sup>6,7</sup> Like many trials in bipolar disorder, generalisability is hampered by small sample size, numerous exclusion criteria (e.g. people with cardiovascular disease) and high dropout rates — in one trial, 50% of all patients did not complete the study.<sup>7</sup> The evidence base for 'real life' effectiveness is limited.

Evidence for maintenance therapy or adjunctive use (e.g. with lithium) is lacking, and ziprasidone is not currently TGA approved for either indication.<sup>8</sup> One unpublished trial failed to find a benefit when ziprasidone was added to lithium therapy.<sup>8</sup>

### Dosing is twice daily with food

Unlike most other atypical antipsychotics, ziprasidone must be taken twice daily with food. Absorption of ziprasidone may be significantly reduced if taken without food.<sup>8</sup> Ensure that people taking ziprasidone are aware of these requirements, especially if switching from another antipsychotic, most of which are dosed once daily without food. Check compliance before increasing dose if symptoms do not improve.

### Safety issues

Common adverse effects with ziprasidone include headache, sedation, somnolence, dizziness, extrapyramidal symptoms and nausea.<sup>8,9</sup>

Safety data on use in mania beyond 3 weeks is limited and can only be extrapolated from longer term studies of ziprasidone in schizophrenia.<sup>10,11</sup> More experience is needed to adequately characterise its adverse effect profile relative to other atypical antipsychotics.

### Metabolic effects and diabetes

Metabolic effects such as weight gain and lipid changes appear less likely with ziprasidone than with other antipsychotics.<sup>9,10</sup> Whether this means that ziprasidone has a lower risk of new-onset diabetes is uncertain. Observational studies have found an increased incidence of new type 2 diabetes with other atypical antipsychotics (olanzapine, quetiapine, risperidone and clozapine) compared with conventional antipsychotics.<sup>12–14</sup> While no increased risk with ziprasidone has been observed to date, fewer epidemiological data are available

because ziprasidone is a newer drug.<sup>12</sup> The exact mechanism by which antipsychotics increase diabetes risk is uncertain and it is not clear if weight gain alone is the causal factor.<sup>12</sup>

### Extrapyramidal symptoms

Extrapyramidal symptoms (EPS) occur with short-term ziprasidone use — 11% of patients with acute mania developed EPS, compared with 2% for placebo in one 3-week trial.<sup>6</sup> EPS may be more likely in short-term use for mania than with some other atypical antipsychotics, but better data are needed to be sure.<sup>15</sup> In an 18-month schizophrenia trial, there were similar rates of EPS-related discontinuations between atypical antipsychotics (4% with ziprasidone and 2% to 3% with olanzapine, risperidone and quetiapine)\* and no difference was found between antipsychotics in EPS symptom ratings.<sup>10</sup> All atypical antipsychotics can cause EPS, although to a lesser extent than conventional antipsychotics such as haloperidol.<sup>4,16</sup>

### QT prolongation

Before prescribing, consider whether the patient has risk factors for QT prolongation. Ziprasidone prolongs the QT<sub>c</sub> interval.<sup>8,9</sup> The clinical significance of this effect is currently not fully known. While clinical trials have not detected clinically significant QT prolongation<sup>8</sup>, there have been postmarketing reports of torsades de pointes in patients with multiple risk factors taking ziprasidone.<sup>8</sup> Ziprasidone is contraindicated in significant cardiovascular disease, including arrhythmias, and in people with other conditions or taking other drugs that may prolong the QT interval (including some antibiotics, antifungals, antidepressants and anti-arrhythmic agents).<sup>8</sup> Ziprasidone may not be appropriate for people at risk of electrolyte imbalances (e.g. hypokalemia, people taking diuretics), which may increase the risk of QT prolongation. For those at risk of electrolyte imbalances, measure potassium and magnesium levels both before starting ziprasidone and during treatment.<sup>8</sup>

\*Statistical significance was not reported for ziprasidone discontinuations compared with other atypical antipsychotics.

A small but increased risk of sudden cardiac death has been observed for all antipsychotics — consider the individual's cardiovascular risk profile before prescribing an antipsychotic, and an ECG before and shortly after starting antipsychotic treatment.<sup>17,18</sup>

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### Sublingual desmopressin PBS listed: where does desmopressin fit in primary nocturnal enuresis?

Desmopressin sublingual wafer (Minirin Melt, 120 micrograms) is available as a streamlined authority listing for primary nocturnal enuresis from 1 April 2009. Similar to desmopressin tablets and nasal spray, the listing for desmopressin sublingual wafers is restricted to children aged  $\geq$  6 years with primary nocturnal enuresis refractory to an enuresis alarm, or when an enuresis alarm is contraindicated.<sup>1</sup>

### Enuresis alarms are the most effective treatment for bedwetting

An enuresis alarm is the first choice for primary nocturnal enuresis. Alarms are at least as effective as desmopressin, more likely to have a sustained effect, and do not have the risk of serious hyponatraemia.<sup>2,3</sup>

Although alarms require close involvement from a parent or carer in the first few weeks of use, about two-thirds of children with nocturnal enuresis become dry at night when using an enuresis alarm, and about half of children stay dry when the alarm is withdrawn.<sup>2,4</sup> Alarms are usually withdrawn after 14 consecutive dry nights and may be trialled for up to 12–16 weeks.<sup>5</sup>

Several different enuresis alarms are available: pad-and-bell alarms that are placed on the bed, and personal alarms that are worn between pairs of underpants. Choice is determined by the child's preference and by cost — there is insufficient evidence to show any one alarm is more effective than another.<sup>2</sup>

Desmopressin acts faster than alarms at reducing the number of wet nights in the first week of treatment, but this advantage does not persist.<sup>6</sup> Relapse rates after stopping desmopressin are similar to those for placebo and higher than for alarms.<sup>6</sup> Desmopressin may have a role in special circumstances, such as short-term use when sleeping away from home.<sup>3,5</sup>

Discuss simple behavioural strategies with the child and their parent or carer. Although there is insufficient evidence to prove effectiveness, some of these may help, are not associated with side effects, and may be preferred by children and parents.<sup>7,8</sup>

### **Sublingual wafers may be easier to take than oral tablets**

Desmopressin sublingual wafer can be taken without water, which may make it easier for some children to take.<sup>9</sup> A single desmopressin 120 micrograms sublingual wafer has an equivalent bioavailability<sup>10</sup> and efficacy to that of a single desmopressin 200 micrograms tablet.<sup>9</sup> There is no difference in the safety profile for the two formulations at recommended doses.<sup>9</sup>

### **Reserve nasal desmopressin for when oral or sublingual formulations cannot be taken**

The nasal formulation of desmopressin is more likely to cause hyponatraemia and seizures than oral formulations (15 cases versus 6 cases per 100,000 years of patient exposure for nasal versus oral formulations).<sup>11</sup>

Hyponatraemia is a rare but serious adverse effect of desmopressin, which may present as anorexia, nausea

and vomiting, difficulty concentration, confusion, lethargy, agitation, headache, and seizures.<sup>11</sup>

Use the nasal formulation only when oral or sublingual desmopressin use is not feasible for primary nocturnal enuresis.<sup>12</sup> Children taking nasal desmopressin for primary nocturnal enuresis are heavily represented in reports of severe hyponatraemia and seizures with desmopressin.<sup>11,13</sup>

### **Minimise risk of hyponatraemia with desmopressin**

If prescribing desmopressin for primary nocturnal enuresis:

- use cautiously and monitor serum sodium levels in children with conditions that may increase the risk of hyponatraemia or water intoxication (e.g. systemic infections, gastroenteritis, syndrome of inappropriate ADH secretion [SIADH])<sup>10</sup>
- reserve the nasal formulation for when an oral or sublingual formulation is not feasible<sup>11,12</sup>
- avoid concomitant use with medicines known to induce SIADH (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, carbamazepine).<sup>10</sup>
- avoid NSAIDs, as they may induce water retention<sup>10</sup>
- advise children and their parents or carers that they can help to minimise the risk of hyponatraemia by:
  - limiting the child's fluid intake for 1 hour before and 8 hours after taking desmopressin<sup>10</sup> — parents or carers may need to closely watch the ingestion of fluid by their child after dosing
  - avoiding excessive fluid ingestion at all times<sup>3</sup>
  - stopping the medicine if the child develops symptoms of water retention (eg, headache, nausea, vomiting, weight gain or convulsions) and reporting these promptly to their doctor<sup>14</sup>
  - stopping the medicine temporarily if the child develops vomiting or diarrhoea from any cause, to allow recovery of normal fluid balance.<sup>3,10</sup>

### **Review need for desmopressin within 3 months of starting treatment**

The benefit of desmopressin is not sustained after stopping, but spontaneous remission of bedwetting does occur. Assess for remission regularly to determine

the need for ongoing treatment. The intended duration of desmopressin sublingual wafer for primary nocturnal enuresis is up to 3 months.<sup>10</sup> Consider capping the number of repeats to ensure an assessment takes place within this period. To assess whether bedwetting has resolved, stop desmopressin and wait a week before reviewing the number of dry nights.<sup>3</sup>

### Resources on bedwetting for parents and children

Resources for parents and children on the management of bedwetting are available at [www.bladderbowel.gov.au](http://www.bladderbowel.gov.au). These include a series of booklets, updated in 2008 (*Sleepover, Watertight, and The Dry Night*), which provide advice on behavioural therapies, alarms, and the place of medicines.

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### Risedronate (Actonel, Actonel Once-a-Week) for corticosteroid-induced osteoporosis

The PBS listing for risedronate (Actonel and Actonel Once-a-Week) and risedronate with calcium (Actonel Combi) has been extended to people with corticosteroid-induced osteoporosis (CIO) who are on long-term high-dose corticosteroid therapy. Eligible people must have been taking high-dose corticosteroids ( $\geq 7.5$  mg/day prednisolone or equivalent) for at least 3 months and have a bone mineral density (BMD) T-score of  $\leq -1.5$ .

Bone loss is worst in the first year of corticosteroid therapy.<sup>1,2</sup> To minimise bone loss, use the smallest possible dose of corticosteroid for the shortest possible time.<sup>1,2</sup> Prescribe at least 1000 mg calcium daily and ensure adequate vitamin D intake.<sup>3</sup>

The risk of a vertebral or hip fracture increases rapidly after beginning corticosteroid treatment but declines within a year of stopping therapy.<sup>1,2</sup>

### Limited data on fracture prevention in people with corticosteroid-induced osteoporosis

No trial in people with corticosteroid-induced osteoporosis has used fracture as a primary endpoint or reported a significant reduction in incident fracture among people taking risedronate, compared with placebo.<sup>4–7</sup> However, meta-analysis of fracture data shows a significant decrease in vertebral fracture risk (relative risk 0.33, 95% confidence interval 0.14 to 0.80) among people with corticosteroid-induced osteoporosis taking risedronate 5 mg daily.<sup>8</sup> There was no significant reduction in vertebral fracture risk among people taking risedronate 2.5 mg daily or in non-vertebral fracture risk in people taking either 2.5 mg or 5 mg daily.<sup>8</sup>

### Risedronate can maintain or improve BMD in people using corticosteroids

In clinical trials, BMD levels deteriorated among people taking placebo but remained steady, or occasionally improved, among those taking risedronate 2.5 mg or 5 mg.<sup>4-7</sup> People taking risedronate 5 mg appear to be more likely to have significantly higher BMD values than those on risedronate 2.5 mg or placebo.<sup>4-7</sup>

One trial followed women taking risedronate 2.5 mg daily for 2 years. Women taking risedronate had significantly higher lumbar spine and femoral trochanter BMD than those receiving placebo. A year after stopping therapy, the risedronate group still had significantly higher lumbar spine BMD than the placebo group, but femoral trochanter BMD was similar to that in the placebo group.<sup>5</sup>

### Minimise gastrointestinal effects with correct administration

Instruct patients to take risedronate early in the morning on an empty stomach. They should swallow the risedronate tablet whole with a full glass of water and remain upright for 30 minutes after the dose to minimise adverse gastrointestinal effects.<sup>3</sup>

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### Zoledronic acid (Aclasta) listing extended to osteoporosis in postmenopausal women

From 1 April 2009 the PBS listing for zoledronic acid (Aclasta) will include treatment of osteoporosis in any postmenopausal woman aged  $\geq 70$  years who has a bone mineral density (BMD) T-score  $\leq -3.0$ . Previously, the listing was only for osteoporosis in women with a fracture, and in men with a hip fracture.

An update of the *NPS RADAR* review of zoledronic acid (Aclasta) for osteoporosis is available on-line at [www.npsradar.org.au](http://www.npsradar.org.au) and in *Medical Director* and *Genie* prescribing software.

Zoledronic acid is given as an annual intravenous infusion. It is important to inform patients starting zoledronic acid that they will need to continue with daily calcium and vitamin D supplements.

Before prescribing zoledronic acid, check if patients have already received an infusion (e.g. in hospital). If oral bisphosphonates were previously used, these must be stopped before starting zoledronic acid.

Adverse effects include acute-phase reactions, such as fever, myalgia, flu-like illness and headache, within 3 days of infusion. Like other bisphosphonates, zoledronic acid may cause hypocalcaemia, and has been associated with renal dysfunction, inflammatory eye disorders, osteonecrosis of the jaw and, possibly, atrial fibrillation.