

Timely, independent information about new drugs

Dabigatran (Pradaxa) for preventing venous thromboembolism after hip or knee replacement surgery

New product PBS listed April 2010

01

Nebivolol (Nebilet) for chronic heart failure

New product PBS listed March 2010

06

Methylnaltrexone injection (Relistor) for opioid-induced constipation in palliative care

New product PBS listed March 2010

11

In Brief

Rizatriptan (Maxalt) 10 mg wafers for migraine and revised listings for other 5HT₁ agonists ('triptans') — Albendazole (Zentel) listing extended to treat hookworm and strongyloidiasis — Postmarketing reports of acute pancreatitis with sitagliptin products (Janumet, Januvia) — Authority listing for terbinafine extended to children and adolescents — Extended PBS listings for zoledronic acid 5 mg (Aclasta)

15

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

Hot on the heels of the *NPS RADAR* review of rivaroxaban (Xarelto [August 2009]) comes a review of another new oral anticoagulant, dabigatran (Pradaxa). Both drugs are approved and PBS listed only for short-term use after total hip or knee replacement. Each provides an oral alternative to daily subcutaneous enoxaparin (Clexane), the most commonly used anticoagulant after hip or knee replacement.

The place of dabigatran and rivaroxaban relative to mechanical and other pharmacological measures is set out in the recent National Health and Medical Research Council's *Clinical practice guideline for the prevention of venous thromboembolism in patients admitted to Australian Hospitals*. The guideline notes that evidence supports the use of low molecular weight heparins, fondaparinux, dabigatran and rivaroxaban for thromboprophylaxis after total hip or knee replacement. Bleeding is the most important potential harm of each. When pharmacological thromboprophylaxis is appropriate, differences in precautions and contraindications, drug interactions, cost, convenience and availability will all influence choice of drug. The relative lack of information about long-term or rare side effects of rivaroxaban and dabigatran is also an important consideration.

Importantly, the guideline advises that decisions about thromboprophylaxis be made in consultation with patients, taking into account their preferences

and perceptions of risk, to help ensure the acceptability of choices and therefore support adherence. Health professionals working with patients who are considering taking dabigatran or rivaroxaban can use *Medicine Update* as a tool for discussing the need for, and choices between, therapies to prevent venous thromboembolism. *Medicine Update* is an NPS publication written for consumers, providing an independent assessment of new medicines.

Medicine Update also provides information about safe and effective use of new medicines. General practitioners and pharmacists prescribing or dispensing rivaroxaban or dabigatran can give a copy of the relevant *Medicine Update* article to patients, along with the consumer medicine information leaflet, as a reminder of their verbal advice. In particular, *Medicine Update* describes the duration of therapy with rivaroxaban or dabigatran after hip or knee surgery — a potential point of confusion for people who have been instructed to visit their doctor for a prescription after discharge.

You can find the *NPS RADAR* reviews for dabigatran and rivaroxaban on our website at www.npsradar.org.au, or in your prescribing software if you are a Medical Director or Genie user. *Medicine Update* is also on our website, at www.nps.org.au/medicineupdate.

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Timely, independent information about new drugs

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Dabigatran (Pradaxa) for preventing venous thromboembolism after hip or knee replacement surgery

(da-BIG-a-tran)

01

Summary

- Dabigatran is a direct thrombin inhibitor oral anticoagulant.
- Dabigatran is approved for short-term use after hip or knee replacement surgery.
- The recommended duration of therapy is 10 days after knee replacement and 28–35 days after hip replacement.
- Dabigatran appears to have similar efficacy to that of enoxaparin 40 mg once daily after knee or hip replacement, although a clinically important difference between the two drugs cannot be completely ruled out.
- Dabigatran, rivaroxaban and fondaparinux all appear to have broadly similar efficacy although this has not been tested in head-to-head trials.
- Bleeding rates with dabigatran are similar to those with enoxaparin.
- Advise patients about the risk of bleeding.
- Dabigatran is contraindicated in hepatic impairment that is expected to have an impact on survival or in severe renal impairment (creatinine clearance < 30 mL/min).

PBS listing

Authority required

Preventing venous thromboembolism (VTE) in people undergoing total hip or total knee replacements.

The listing provides for a maximum dispensed quantity of 60 capsules for hip replacement and 20 capsules for knee replacement.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing dabigatran on a cost-minimisation basis — that is, similar efficacy and cost — compared with enoxaparin. The decision was based on 2 non-inferiority trials — 1 in people undergoing hip replacement¹ and another in people undergoing knee replacement.²

Place in therapy

Dabigatran is an oral direct thrombin inhibitor approved for short-term use to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE) after hip or knee replacement surgery. The recommended duration of therapy is 10 days after knee replacement³ and 28–35 days after hip replacement.^{3,4} Dabigatran appears to be similar in efficacy to enoxaparin, a low molecular weight heparin (LMWH) that is currently the most commonly prescribed therapy. Dabigatran, rivaroxaban (an oral factor Xa-inhibitor anticoagulant) and fondaparinux appear to be similarly efficacious although this has not been tested in head-to-head trials.

Australian guidelines recommend LMWH, fondaparinux, dabigatran or rivaroxaban for thromboprophylaxis after total hip or knee replacement.⁴ These agents differ in their interactions and precautions in special populations (such as hepatic or renal impairment). These factors,

in addition to hospital availability, patient preference and patient ability to swallow oral medications after surgery, will guide the choice of drug for many people. However, dabigatran and rivaroxaban should be used more cautiously, as they are new drugs and there are insufficient data to characterise potential rare or long-term adverse effects.⁴

Dabigatran is an oral anticoagulant

The prodrug dabigatran etexilate is converted to dabigatran, a direct thrombin inhibitor, in the body.

Dabigatran is approved only for short-term use after hip or knee replacement surgery. There are trials evaluating dabigatran for the treatment of acute VTE and for stroke prevention in atrial fibrillation but these indications are not approved in Australia or overseas.^{5,6}

Dabigatran appears to have similar efficacy to that of enoxaparin 40 mg once daily after knee or hip replacement

Dabigatran 150 mg and 220 mg once daily have been compared with enoxaparin 40 mg once daily after hip or knee replacement.^{1,2} At these doses, dabigatran was no worse than enoxaparin on a primary composite endpoint of venographically detected thromboembolism*, symptomatic DVT or PE, and death from any cause (Table 1).

The margins used to test for non-inferiority in both trials were relatively large. In the trials the number of primary events in the dabigatran arm could be up to 7.7% higher than in the enoxaparin arm of the hip replacement trial and 9.2% higher than in the enoxaparin arm of the knee replacement trial before dabigatran was considered to be inferior to enoxaparin.^{1,2} However, the PBAC noted in a previous submission that a 4–5% increase in the number of primary events could be clinically important.⁷ The number of primary events for the 220 mg dabigatran dose fell within this range for both the hip replacement and the knee replacement trial. However, the trials were not designed to test whether there is a difference of this magnitude (i.e. 4–5%), so a clinically important difference cannot be completely ruled out.

* While venographically detected thromboembolism is an accepted surrogate outcome in VTE trials, not all cases are clinically significant.

Most of the primary events in the trials were venographically detected thromboemboli. A secondary endpoint, which may better reflect clinical relevant events, was major VTE (proximal DVT or non-fatal PE) or VTE-related death. There were similar numbers of symptomatic DVT, PE or VTE-related deaths in both arms of the hip and knee replacement trials (Table 1).

In another trial that tested dabigatran against the North American regimen of enoxaparin 30 mg twice daily, dabigatran was less efficacious than enoxaparin after knee replacement.⁸ However, this enoxaparin dosage is more intensive than the 40 mg once daily recommended by Australian guidelines.^{9,10}

Use graduated compression stockings as well as antithrombotic therapy

To further reduce the risk of VTE, surgery patients should wear graduated compression stockings from the time of admission until they return to their usual level of mobility.^{4,11}

Participants in the dabigatran trials were permitted to use compression stockings.^{1,2,8,12} However, information on how commonly stockings were used was not provided. Use of intermittent compression devices was not permitted.

Table 1: Proportion of people who had a primary or secondary outcome in trials of dabigatran in hip and knee replacement

	Dabigatran		Enoxaparin
	150 mg	220 mg	40 mg
Hip replacement¹ (n = 2651)*			
Primary outcome [†]	8.6%	6.0%	6.7%
Secondary outcome [‡]	4.3%	3.1%	3.9%
Knee replacement² (n = 2101)*			
Primary outcome [†]	40.5%	36.4%	37.7%
Secondary outcome [‡]	3.8%	2.6%	3.5%

* Between 23% and 30% of randomised patients did not have an evaluable venogram. Therefore, n values refer to the number of patients with an evaluable venogram, not the number initially randomised.

[†] Venographically detected or symptomatic DVT/PE or death from any cause.

[‡] Symptomatic DVT/PE or VTE-related death.

Dabigatran, rivaroxaban, low molecular weight heparins and fondaparinux differ only slightly in effectiveness

Evidence-based guidelines from the UK National Institute for Health and Clinical Excellence (NICE) reported broadly similar efficacy for dabigatran, rivaroxaban, LMWHs and fondaparinux after hip or knee replacement.^{11,13,14} Aspirin, warfarin and unfractionated heparin are not recommended for these indications, as they appear to be less effective than the other agents for preventing VTE after elective surgery.^{4,11}

No clinical trials have directly compared dabigatran with rivaroxaban or fondaparinux for VTE prevention. NICE made their assessment on the basis of indirect comparisons and cost-effectiveness modelling.

Safety issues

Bleeding rates with dabigatran are similar to those with enoxaparin. The incidence of common adverse effects is also similar, although wound secretion is significantly more common among people taking dabigatran.³ There are insufficient data to characterise rare or long-term adverse effects.

People at high risk of bleeding were excluded from trials. Do not use dabigatran in these people (e.g. those with severe uncontrolled hypertension, thrombocytopenia or bleeding disorders), in people with severe renal impairment or in those taking strong P-glycoprotein inhibitors.^{3,10}

Combining dabigatran with other anticoagulants or antiplatelets is not recommended.³

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Rate of major bleeding is similar to that with enoxaparin

People at high risk of bleeding were excluded from trials. Major bleeding rates for both doses of dabigatran were similar to those for 40 mg enoxaparin in either hip or knee replacement surgery (Table 2).

There is no antidote to dabigatran-induced bleeding.³ Stop dabigatran and treat bleeding symptomatically. Arrange hospital management if necessary.

Take care combining with antiplatelet drugs or NSAIDs

Monitor people for signs of bleeding if they are taking dabigatran in conjunction with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).^{3,10} Combining dabigatran with other anticoagulants or antiplatelets, including clopidogrel, is not recommended.³

Trial participants were allowed to take low-dose aspirin (< 160 mg) or cyclo-oxygenase-II (COX-2) selective NSAIDs.^{1,2,12} However, there is no published information on how commonly these medicines were taken or on bleeding rates associated with their use.

Combining with P-glycoprotein inhibitors can increase bleeding risk

P-glycoprotein inhibitors may increase plasma concentrations of dabigatran and consequently increase bleeding risk. The pro-drug dabigatran etexilate (but not dabigatran) is a substrate of P-glycoprotein. Use the 150 mg dose of dabigatran if a person is taking amiodarone. Use dabigatran cautiously and monitor for signs and symptoms of bleeding if a person is taking other P-glycoprotein inhibitors (e.g. cyclosporin, clarithromycin, itraconazole, ketoconazole, ritonavir, saquinavir, tacrolimus or verapamil).³

Verapamil may increase the concentration of dabigatran if taken at the same time of day, increasing the risk of bleeding. If possible, avoid this combination. The manufacturer advises that verapamil should not be started during dabigatran therapy.³ If dabigatran is added to verapamil therapy, it must be given 2 hours before verapamil to avoid this interaction.^{3,10}

Table 2: Major bleeding rates*

	n	Dabigatran		Enoxaparin
		150mg	220mg	40mg
Hip replacement ¹	3463	1.3%	2.0%	1.6%
Knee replacement ²	1976	1.3%	1.5%	1.3%

* Major bleeding events were defined as those that resulted in: a reduction in haemoglobin levels of at least 20 g/L; transfusion of at least 2 units of blood; fatal retroperitoneal, intracranial, intraocular or intraspinal bleeding; and bleeding warranting treatment cessation or reoperation.

An increased risk of rare adverse events has not been ruled out

Use dabigatran and rivaroxaban (the other new oral anticoagulant) cautiously, as there is a lack of postmarketing surveillance data.⁴

People with liver disease or elevated liver enzyme levels (> 2 times the upper limit of normal) at baseline were excluded from trials of dabigatran. A drug in the same class as dabigatran, ximelagatran, was withdrawn after reports of severe liver damage.^{15,16} However, rates of elevated liver enzyme levels with dabigatran were:

- lower than that reported in people taking enoxaparin after hip replacement¹
- similar to those reported in people taking enoxaparin after knee replacement²
- similar to those reported in people taking warfarin for acute VTE or atrial fibrillation.^{5,6}

Dosing issues

Dabigatran should be taken for 10 days after knee replacement and for 28–35 days after hip replacement.

Treatment is started with a single capsule (75 mg or 110 mg) 1–4 hours after surgery. The dose is then increased to 2 capsules taken together once a day.³

Most discharged patients will be taking 220 mg dabigatran (2 × 110 mg capsules) once daily.³ However, people with moderate renal impairment (creatinine clearance 30–50 mL/min) will be taking a 150 mg dose (2 × 75 mg capsules).³

In pharmacokinetic studies, people with moderate renal impairment had an exposure to dabigatran that was almost 3 times higher than in people without renal insufficiency. This is likely to increase the risk of bleeding.³ Only about 5% of people in the

randomised trials had moderate renal impairment⁷ so it is not known whether using the 150 mg dose instead of the 220 mg dose reduces this increased bleeding risk. Until more data become available an alternative anticoagulant, such as enoxaparin, may be a better option in moderate renal impairment.

Some patients will require a prescription soon after hospital discharge

Some hospital patients will be advised to obtain a prescription from their general practitioner after discharge to cover the remaining duration of dabigatran therapy. Prescribers will need to take into account the number of capsules the hospital has already provided and the intended duration of therapy when selecting the pack size and giving instructions to the patient.

The listing provides for a maximum dispensed quantity of 60 capsules for hip replacement and 20 capsules for knee replacement.

Two pack sizes are available for people undergoing hip replacement — a 60-capsule pack and a 10-capsule pack. People undergoing hip replacement should be treated for a maximum of 35 days.⁴ The 60-capsule pack (sufficient for 30 days' treatment) should not be broken but the 10-capsule pack may be broken to allow the exact number of capsules for the remaining duration of treatment to be dispensed.

Only the 10-capsule pack is listed for people undergoing knee replacement. People undergoing knee replacement should be treated for 10 days, so they are likely to need more than 1 pack to ensure this. The pack may be broken to allow the exact number of capsules to be dispensed.

If the exact number of capsules is not dispensed there may be surplus capsules, as pack sizes will not always match the recommended treatment duration. Advise patients not to take capsules for longer than the recommended duration of treatment.

Information for patients

Advise patients and carers:

- to consult a doctor before using non-prescription medicines containing aspirin or NSAIDs. Paracetamol can be used for minor ailments
- to consult a doctor if they have any prolonged or excessive bleeding or signs of internal bleeding, such as unexplained bruising, blood in the urine or black stools
- to take 2 capsules at about the same time each day. Swallow capsules whole with water; they can be taken with or without food
- that if they miss a dose, not to take a double dose to make up for it

- not to take dabigatran supplied by the hospital and by their GP simultaneously
- to continue to wear compression stockings if recommended
- to tell their doctor, dentist or pharmacist at each consultation that they are taking dabigatran.

Discuss the Pradaxa consumer medicine information (CMI) leaflet with the patient.

Medicine Update

An NPS *Medicine Update* leaflet on dabigatran is available for consumers. *Medicine Update* helps consumers to ask the right questions about new medicines, and helps them compare the potential benefits and harms of a new medicine with other medicines.

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Nebivolol (Nebilet) for chronic heart failure

(ne-BIV-o-lol)

Summary

- Nebivolol is a new selective beta₁-receptor antagonist for treating chronic heart failure.
- Nebivolol is an alternative to bisoprolol, carvedilol, and controlled-release metoprolol but has less robust evidence of survival benefit.
- Although the major trial with nebivolol was conducted in older people (≥ 70 years), there is no evidence that nebivolol is more effective in any age group than other beta blockers used in heart failure.
- Nebivolol is contraindicated in people with hepatic impairment and should be avoided in severe renal impairment.
- Start nebivolol at a low dose (1.25 mg once daily) and slowly titrate to the maximum tolerated dose (up to 10 mg once daily).
- As for other beta blockers, worsening heart failure, bradycardia and dizziness are common during dose titration.
- Avoid stopping nebivolol abruptly, as this can worsen heart failure, or precipitate angina, myocardial infarction or ventricular arrhythmia in people with ischaemic heart disease.

PBS listing

Authority required (streamlined)

For people with moderate to severe heart failure who are stable on standard therapy, which must include an ACE inhibitor or an angiotensin II-receptor antagonist, if tolerated.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing of nebivolol on a cost minimisation basis — that is, similar efficacy and cost — compared with bisoprolol, carvedilol and metoprolol.¹

The decision was based on 3 head-to-head trials with carvedilol that compared effects on surrogate measures of heart failure. The PBAC accepted that nebivolol caused similar improvements in surrogate measures (change in left ventricular ejection fraction [LVEF], change in 6-minute walk test and New York Heart Association [NYHA] class improvement) to those of carvedilol, and had a comparable safety profile. The PBAC also considered an indirect comparison with other beta blockers (bisoprolol, carvedilol and metoprolol) versus placebo for evidence of patient-relevant outcomes in heart failure.


Place in therapy

Nebivolol is a selective beta₁-receptor antagonist. It is effective in chronic heart failure when used as an adjunct to ACE inhibitors (or angiotensin II-receptor antagonists) and/or diuretics.^{2–6} Nebivolol is also approved for hypertension but is not PBS listed for this indication.

Nebivolol has been available in Europe for treating hypertension for more than 10 years, and for heart failure for about 2 years. It has been available in the US for hypertension for 2 years. The US Food and Drug Administration's advisory panel recently voted against approval to register nebivolol for heart failure in the US based on insufficient evidence of effectiveness.^{7,8}

Evidence for functional improvement in heart failure is comparable to that of other beta blockers, but nebivolol has less robust evidence of survival benefit. Although the trial investigating patient-relevant outcomes with nebivolol was conducted in an older population than other beta-blocker trials, there is no evidence that nebivolol is more effective in any age group than other beta blockers used in heart failure.

Nebivolol is an alternative to other beta blockers used in heart failure but has less robust evidence of survival benefit

Clinical trials suggest that nebivolol has a similar effect on surrogate outcomes in heart failure to that of bisoprolol, carvedilol, or metoprolol. Nebivolol provides improvements in functional capacity (LVEF % improvement and distance walked over 6 minutes) and symptom severity (improvement in New York Heart Association class ) comparable to those of carvedilol, with no major differences in the adverse-effect profiles of the two drugs.²⁻⁴

However, evidence for the effect of nebivolol on rate of hospitalisation or death in people with heart failure is less robust than that for other beta blockers. In the only trial to investigate its effects on morbidity and survival (SENIORS), nebivolol marginally reduced the risk of a composite outcome of death or cardiovascular hospitalisation, compared with placebo. But, unlike similar trials with other beta blockers, nebivolol had no effect on death rate alone or on the rate of cardiovascular hospitalisation alone.⁵ No trials have directly compared morbidity and mortality outcomes in heart failure between nebivolol and other beta blockers.

Weighing up the benefits of nebivolol against those of other beta blockers is hampered by differences in study populations

The population studied in the major trial for nebivolol was intended to represent older people with heart failure in the community, a group not well studied in other beta-blocker trials.⁹ People in the SENIORS trial were, on average, older and more were women than in other beta-blocker trials. Unlike people in other major beta-blocker trials¹⁰⁻¹², a proportion had preserved systolic ventricular function (see Table 1).

The trial investigated the efficacy and safety of nebivolol compared with placebo in people aged ≥ 70 years with a clinical history of heart failure (discharged from hospital in the previous 12 months with a diagnosis of congestive heart failure or with an LVEF $\leq 35\%$ in the previous 6 months). Nebivolol was started at 1.25 mg daily and titrated as tolerated to a maximum of 10 mg once daily with a mean follow-up of 21 months.

Compared with placebo, nebivolol marginally reduced the proportion of people who experienced the composite endpoint of death or cardiovascular hospital admission (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74 to 0.99). However, there was no difference between nebivolol and placebo on death rate alone.⁵ In contrast, other major trials of beta blockers have consistently found more than a 30% reduction in death rate after 1 year of treatment¹³ (see Table 2).

Differences in patient populations may account for the discrepancy in survival benefit between nebivolol and other beta blockers. A post hoc analysis of a subgroup from SENIORS, which more closely matched other trial populations (< 75.2 years with an ejection fraction $\leq 35\%$, $n = 684$), found a similar mortality benefit with nebivolol to that of other beta blockers (HR 0.62, 95% CI 0.43 to 0.89).⁵ However, the results of this unplanned analysis should be interpreted with caution. Further research is needed to confirm the survival benefit of nebivolol.

Table 1: Patient characteristics in major trials of beta blockers in heart failure^{5,10-12}

Drug and trial	Age mean (years)	Female (%)	LVEF mean (%)
Nebivolol SENIORS $n = 2128$	76	38	36
Carvedilol COPERNICUS $n = 2289$	63	21	20
Bisoprolol CIBIS-II $n = 2647$	61	19	28
Metoprolol-CR MERIT-HF $n = 3991$	64	23	28

Table 2: Effect of beta blockers on all cause mortality in heart failure^{5,10-12}

Trial	Drug	Treatment effect* (95% CI)
SENIORS	Nebivolol	0.88 (0.71 to 1.08) [†]
COPERNICUS	Carvedilol	0.65 (0.52 to 0.81)
CIBIS-II	Bisoprolol	0.66 (0.54 to 0.81)
MERIT-HF	Metoprolol-CR	0.66 (0.53 to 0.81)

* Hazard ratios with 95% confidence intervals, except for MERIT-HF, reported as relative risk
† Not significant

 Refer to this review at www.npsradar.org.au for more information about New York Heart Association classification of heart failure.

Nebivolol is no more effective than other beta blockers in older people

Despite the SENIORS trial population being markedly older than people in other beta-blocker trials, there is no evidence to suggest that nebivolol is more effective in this age group than other beta blockers. In the SENIORS population, the effect of nebivolol appeared to be independent of age, gender, or LVEF.¹⁴ Nebivolol's vasodilatory properties (thought to be due to nitric oxide modulation) are of unknown clinical relevance.¹⁴

Safety issues

The adverse-effect profile of nebivolol is similar to those of other beta blockers used in heart failure.^{2,3,5,6} The most common adverse effects reported in the SENIORS trial for nebivolol and placebo, respectively, were:¹⁴

- bradycardia (11% versus 2%)
- dizziness (14% versus 13%)
- hypotension (7% versus 7%)
- fatigue (6% versus 5%).

Worsening heart failure was reported in about 20% of patients in each group.¹⁴ Most adverse events with nebivolol were reported during the titration period (see below).¹⁴

Nebivolol is contraindicated in people with hepatic impairment, because of limited experience in this population. Patients with liver enzyme levels ≥ 3 times the upper limit of normal were excluded from the SENIORS trial.⁹ Avoid use in people with severe renal impairment (serum creatinine concentration ≥ 250 micromol/L), as there is no experience in these patients.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Monitor vital signs closely when starting or titrating nebivolol

Do not start nebivolol in people who have had acute heart failure in the past 6 weeks.¹⁴ Assess heart rate, blood pressure and clinical status before starting nebivolol and before increasing the dose. Do not increase the dose unless the patient is stable (see below). Discuss each of the common adverse effects of nebivolol with the patient and what to do if they experience them (see Information for patients).

The manufacturer recommends that people starting nebivolol or receiving a dose increase are observed under the supervision of an experienced doctor for at least 2 hours to ensure that they remain clinically stable¹⁴, which is consistent with the SENIORS protocol. A similar recommendation was included in the product information for other beta blockers when first approved for heart failure, but has since been removed.¹⁵ There appears to be no pharmacological reason why monitoring during the dose titration of nebivolol should be different from that of other beta blockers used in heart failure.

Worsening heart failure, bradycardia and dizziness can sometimes be managed without stopping nebivolol

If worsening heart failure or intolerance (e.g. low heart rate, hypotension, dizziness) is experienced during dose titration, consider reducing the dose stepwise and extending the dose titration interval (see Dosing issues).¹⁴ Adjusting the dose of concomitant diuretic or ACE inhibitor first may be more appropriate for some symptoms (e.g. pulmonary oedema).^{16,17} Try not to stop nebivolol abruptly, because this can worsen heart failure, or precipitate angina, myocardial infarction or ventricular arrhythmia in people with ischaemic heart disease.¹⁴ To stop nebivolol, gradually reduce the dose by halving it each week.¹⁴

However, if symptoms are severe (e.g. severe hypotension, worsening of heart failure with acute pulmonary oedema, cardiogenic shock, symptomatic

bradycardia or AV block), consider stopping nebivolol and closely monitor the patient. Hospital admission is probably indicated in such cases.

Limited experience in severe heart failure

Most patients treated with nebivolol in the SENIORS trial were NYHA grade II or III (94%), and only about 2% had severe heart failure (NYHA grade IV). Another placebo-controlled study with nebivolol had a similar proportion of people with NYHA grade IV heart failure.⁶ Head-to-head trials with nebivolol have excluded people with severe heart failure.²⁻⁴

Some SSRIs may increase the risk of adverse effects with nebivolol

Cytochrome P450 2D6 inhibitors such as paroxetine and fluoxetine may increase plasma concentrations of nebivolol. This could increase the risk of bradycardia and other adverse effects¹⁴, particularly if cytochrome P450 2D6 inhibitors are started after titrating the nebivolol dose.

Dosing Issues

Start with 1.25 mg once daily for 1–2 weeks. Titrate up in a stepwise manner to the maximum tolerated dose (up to 10 mg daily).¹⁴ Nebivolol can be taken with or without food.¹⁴

Titrate slowly according to patient tolerance

If the starting dose is tolerated and the patient is stabilised, increase the dose to 2.5 mg once daily for 1–2 weeks*, then, as tolerated, to 5 mg once daily for 1–2 weeks, then, as tolerated, to the maximum of 10 mg once daily.

Note that nebivolol is also indicated for hypertension, but has a different dosing regimen for this indication.

Individual tolerance may vary

In the SENIORS trial, 68% of patients treated with nebivolol reached a dose of 10 mg daily and a further 12% reached 5 mg daily.⁵ No special dosage

adjustment is required in older people, in people with mild to moderate renal impairment, or in poor metabolisers of nebivolol.[†] The dose of nebivolol should always be titrated to the maximum tolerated dose (no more than 10 mg once daily) for the individual. Poor metabolisers, who have about 1.4 times the plasma concentration of nebivolol and active metabolites as extensive metabolisers, may not tolerate nebivolol as well and may require a lower ultimate dose.

Information for patients

Advise patients¹⁸:

- that nebivolol improves symptoms of heart failure and reduces the risk of dying or being admitted to hospital with heart problems
- that initial worsening of some symptoms of heart failure is common. Patients should promptly see their doctor if they experience breathlessness, tiredness, or increased swelling in their legs or stomach
- to go immediately to the Emergency department at their local hospital if they experience severe lightheadedness, dizziness or fainting
- that they will start on a low dose that is then gradually increased over a number of weeks to the dose best for them
- to stand up slowly when getting out of bed or up from a chair, to lessen dizziness or lightheadedness
- that they must drink enough water when exercising and in hot weather, to avoid sudden drops in blood pressure (lightheadedness)
- that they must not stop taking nebivolol without speaking to their doctor, because abruptly stopping could make their condition worse.

Discuss the Nebilet consumer medicine information (CMI) leaflet with the patient.

* NICE guideline on heart failure suggests doubling the dose of beta blockers at not less than 2-weekly intervals.¹⁷

† Metabolism of nebivolol depends on cytochrome P450 2D6, which is subject to genetic polymorphism.

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Methylnaltrexone injection (Relistor) for opioid-induced constipation in palliative care

(METH-il-nal-TREX-own)

Summary

- Methylnaltrexone is an option for treating opioid-induced constipation in people receiving palliative care who have not responded to adequately titrated laxatives.
- Methylnaltrexone increases bowel movements without reversing analgesia.
- Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.
- Exclude bowel obstruction before using methylnaltrexone.
- Around 50–60% of people with opioid-induced constipation experience a bowel movement within 4 hours of a single dose of methylnaltrexone. However, around 30% of people may not respond within 24 hours of a single dose.
- The recommended dose varies with weight.
- Only use methylnaltrexone in addition to other therapies that prevent or treat opioid-induced constipation.
- Ensure that toileting facilities are accessible, as bowel movements may occur within 30 minutes of an injection.
- Do not use methylnaltrexone more than once every 24 hours.
- Mild to moderate gastrointestinal adverse effects are common.

11

PBS listing

Authority required

Methylnaltrexone is listed on the palliative care schedule for treatment, in combination with oral laxatives, of opioid-induced constipation that has failed to respond to laxatives.

Initial supply is for 3 doses. If the patient responds, a further 7 doses with up to 3 repeats may be prescribed. Subsequent and continuing supply of a further 7 doses with up to 3 repeats requires a response to methylnaltrexone **and** consultation with a palliative care specialist or service. However, if a palliative care specialist or service is not consulted, supply is limited to a further 7 doses with no repeats for people who have responded to methylnaltrexone.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended methylnaltrexone for listing on the basis of high clinical need. Methylnaltrexone was considered to have acceptable cost-effectiveness compared with placebo.¹

Place in therapy

Methylnaltrexone is an opioid antagonist that, in clinical doses, is unable to cross the blood–brain barrier. Therefore, it can reverse the effect of opioids in the peripheral nervous system and relieve constipation without reversing the analgesic effect of opioids in the central nervous system (CNS).

Methylnaltrexone is only registered for use in palliative care patients with opioid-induced constipation. It is administered as a subcutaneous injection. It may be an option for people who have opioid-induced constipation that has not responded to adequately titrated laxatives, and in whom bowel obstruction has been excluded. Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.

Methylnaltrexone is a quaternary amine derivative of naltrexone

Opioid analgesia is the result of agonist actions on opioid receptors in the CNS.^{2,3} However, constipation is primarily the result of opioid actions on receptors in the bowel.³

Naltrexone is an opioid antagonist that can cross the blood–brain barrier. It may reverse opioid-induced constipation but will also reverse the analgesic effect of opioids in the CNS.^{2,4,5}

Methylnaltrexone is produced by adding a methyl group to naltrexone.⁵ This increases the polarity and lowers the lipid solubility of the molecule, preventing it from crossing the blood–brain barrier when it is given in clinically appropriate doses.^{4,5} As a result, methylnaltrexone does not reverse opioid analgesia.

Methylnaltrexone increases bowel movements in opioid-induced constipation

In placebo-controlled trials, around 50–60% of people in palliative care with opioid-induced constipation defecated within 4 hours of the first dose of methylnaltrexone (Table 1). Around 30% of people did not respond to a single dose of methylnaltrexone after 24 hours.⁶

Almost all trial participants were using laxatives at baseline but had not defecated for more than 48 hours or had had fewer than 3 bowel movements in the

previous week, with no clinically significant defecation in the previous 24 hours.^{6,7} Participants were using a median of 2 classes of laxatives but it is unclear if this was optimal laxative therapy. Adjusting the laxative regimen may have resulted in adequate defecation without the need for methylnaltrexone.

Just over 200 people in these two trials received methylnaltrexone on an ‘as needed’ basis for up to 4 months during open-label extensions of the trials. While more than half of the people who entered the open-label studies withdrew or died — usually because of underlying disease progression — the overall response rate was similar to that achieved during the randomised trials: around 50–60% of participants defecated within 4 hours of receiving methylnaltrexone.^{6,7}

Up to 50% of people may not respond to a particular instance of receiving methylnaltrexone. However, in one trial in which participants received 7 doses of methylnaltrexone or placebo over a 2-week period the response rates were 79% and 46%, respectively.⁷

Methylnaltrexone does not reverse analgesia

Mean pain scores and opioid withdrawal scores among trial participants receiving methylnaltrexone did not change from baseline. No difference in mean pain or opioid withdrawal scores was reported in the methylnaltrexone or placebo groups.^{6,7}

Patients may choose to use lower doses of opioids than necessary for complete analgesia because of unacceptable constipation. It is not known whether the use of methylnaltrexone would allow the opioid dose to be increased in such patients, as no study provided this information.

Continue other therapies to prevent or treat opioid-induced constipation

Trial participants using laxatives at baseline continued to use them throughout the trials of methylnaltrexone.^{6–8}

Laxatives should be routinely prescribed whenever opioids are used.^{9,10} Consider a combined stimulant laxative with stool softener (eg, Coloxyl with Senna).^{2,9} Titrate the dose every few days until comfortable defecation is achieved and increase laxative doses if the opioid dose increases.¹¹

Continue non-drug interventions to prevent or treat opioid-induced constipation. These include ensuring adequate fluid intake, encouraging mobility if possible and encouraging bowel movements at the same time

Table 1: Proportion of trial participants who defecated within 4 hours of the first dose of methylnaltrexone or placebo

	n	% responders		
		Methylnaltrexone 0.15 mg/kg	Methylnaltrexone 0.30 mg/kg	Placebo
Slatkin et al. ⁶	154	62%	58%	14%
Thomas et al. ⁷	133	48%	—	15%

each day.^{2,9} Avoid bulking agents and high-fibre diets in people receiving palliative care.^{2,9}

No studies have compared the efficacy of methylnaltrexone with other pharmacological or non-pharmacological treatments of constipation. No study has investigated whether methylnaltrexone can prevent opioid-induced constipation.

Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.

Safety issues

Common adverse effects include abdominal pain, flatulence, nausea and dizziness.^{6–8,12} Because of the small number of palliative care patients (n = 320) enrolled in trials of methylnaltrexone, information on the full adverse-effect profile remains limited. No trial has lasted longer than 4 months.^{6–8,12}

Bowel obstruction should be ruled out before using methylnaltrexone.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Adverse effects were common but usually mild to moderate

In trials undertaken in palliative care patients, abdominal pain, flatulence, nausea and dizziness were reported more frequently in people taking methylnaltrexone than placebo (Table 2).^{6–8,12} Symptoms were generally reported to be mild or moderate.

There has been 1 death considered to be partly related to the use of methylnaltrexone. A 73-year-old woman with metastatic breast cancer developed severe

Table 2: Commonly increased adverse effects in trials of methylnaltrexone against placebo^{6,7}

Adverse effect	Methylnaltrexone*	Placebo
Abdominal pain	17–38%	4–13%
Flatulence	13–15%	4–7%
Nausea	4–15%	2–7%
Dizziness	4–9%	0–3%

* Methylnaltrexone doses of 0.15 mg/kg or 0.3 mg/kg

diarrhoea, nausea, vomiting and syncope after 3 doses of 0.3 mg/kg methylnaltrexone within a few days. Supportive intervention was limited to comfort measures but rehydration was not attempted. The cause of death was listed as metastatic breast cancer, exacerbated by diarrhoea, subsequent dehydration and cardiovascular collapse.⁶

Dosing Issues

Methylnaltrexone is administered as a subcutaneous injection into the upper arm, thigh or abdomen.¹² Each dose is supplied in a single-use vial containing 12 mg methylnaltrexone in 0.6 mL water. Single-use syringes are also provided in the 7-dose packs.[†] The recommended dose varies with weight (Table 3).

Inject methylnaltrexone as needed but do not use more than once every 24 hours.

Typically, methylnaltrexone is administered every second day but it is possible to wait longer between injections if such frequent dosing is unnecessary.¹² Alternatively, if there has been no bowel movement within 24 hours of an injection, another dose may be administered.¹² However, do not use methylnaltrexone more than once every 24 hours.¹²

Methylnaltrexone can be administered by the patient or a carer. Instructions on preparing and administering a dose of methylnaltrexone are included with each vial or pack of methylnaltrexone. Vials should only be used once: ensure patients and carers understand how to dispose of unused liquid and needles safely. Patient information booklets will be distributed to prescribing doctors and are also available from the sponsor.

Ensure toileting facilities are accessible, as bowel movements may occur within 30 minutes of an injection.^{6,7,12}

Table 3: Recommended dose of methylnaltrexone¹²

Patient weight	Dose	Injection volume
< 38 kg	0.15 mg/kg	Weight (kg) × 0.0075; rounded to nearest 0.1 mL
38–61 kg	8 mg	0.4 mL
62–114 kg	12 mg	0.6 mL
> 114 kg	0.15 mg/kg	Weight (kg) × 0.0075; rounded to nearest 0.1 mL

† Methylnaltrexone is available in a single or 7-dose pack.

Information for patients

- Use methylnaltrexone as needed but do not use more than once every 24 hours.
- Common adverse effects include mild to moderate abdominal pain, nausea and flatulence.
- Use a different site for each injection and do not inject into areas where the skin is tender, bruised, red or hard.¹²
- You may have a bowel movement as soon as 30 minutes after an injection. Ensure that toileting facilities are easily accessible.
- Vials should only be used once: discard unused liquid and needles safely.¹²
- Half of all people who have responded to a dose of methylnaltrexone do so within 4 hours.

Discuss the Relistor (methylnaltrexone) consumer medicine information (CMI) leaflet with the patient.

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In Brief

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

Rizatriptan (Maxalt) 10 mg wafers for migraine, and revised listings for other 5HT₁ agonists ('triptans')

Rizatriptan 10 mg wafers were listed on the Pharmaceutical Benefits Scheme (PBS) as authority required (streamlined) on 1 March 2010 for people with past migraines that have usually failed to respond to analgesics.¹

Rizatriptan has been available overseas for more than 10 years.² All triptans are effective for migraine^{3,4} but individual response cannot be predicted.⁵ If the first triptan fails, try another.

As of 1 April 2010, the PBS restriction for naratriptan, sumatriptan and zolmitriptan has changed: there is no longer a requirement for past migraines to have failed to respond to ergotamine*.⁶ This change brings the restriction into line with that of rizatriptan.

* Injectable dihydroergotamine is the only ergot alkaloid indicated for migraine listed on the PBS.

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Albendazole (Zentel) listing extended to treat hookworm and strongyloidiasis

The streamlined authority listing for albendazole tablets (200 mg) has been extended as of 1 March 2010 to include treatment of strongyloidiasis and hookworm.¹

Strongyloidiasis and hookworm are endemic in tropical and subtropical regions, including Africa, Asia and the Americas. They are also common in Aboriginal and Torres Strait Islander communities in northern Australia.^{2–4}

Albendazole is the treatment of choice for hookworm.^{3,5} In strongyloidiasis, ivermectin (Stromectol) is the treatment of choice but albendazole is an alternative for those in whom ivermectin is unsuitable (see below).^{3,5}

Life cycle

Both hookworms and *Strongyloides stercoralis* infect humans via larvae that penetrate the skin, are carried by the blood to the lungs and then migrate to the small intestine via the trachea and oesophagus. There they become adults and attach themselves to the intestinal wall to feed and lay eggs.^{2,6,7}

Adult hookworms can live in the human body for up to 5–7 years but they are unable to reproduce solely within a human host.⁶ Instead eggs are excreted in faeces, hatch in contaminated soil and then develop into larvae that can infect another person.⁷

In contrast, without adequate treatment *S. stercoralis* infection may be lifelong due to auto-infection. *S. stercoralis* larvae hatch from eggs while still in the intestinal tract. Some of these newly hatched larvae reinfect the host and repeat the cycle while others are passed in the faeces. Excreted larvae can infect other people or develop into free-living adults that continue laying eggs.²

Symptoms

Strongyloidiasis and light hookworm infections are often asymptomatic. However, local itching and rash may occur where larvae penetrate the skin and respiratory symptoms may occur when larvae migrate into the lungs.^{2,7}

In heavy hookworm infections, blood loss where adult hookworms attach themselves to the intestinal wall can cause anaemia.⁶ Other symptoms may include abdominal pain, diarrhoea, loss of appetite, weight loss, and stunted growth and mental development.⁷

Auto-infective *S. stercoralis* larvae can disseminate throughout the body and may carry intestinal bacteria to other parts of the body.^{2,8} Disseminated disease is potentially fatal and poses the greatest risk to people who are immunocompromised or taking corticosteroids.⁸ People with disseminated disease may present with abdominal pain, distension, shock, pulmonary and neurological complications and septicaemia.²

Diagnosis and treatment

Use a single dose of albendazole to treat hookworm. Albendazole is less effective than ivermectin in treating strongyloidiasis and should be reserved for those in whom ivermectin is not recommended (Table 1).^{3,9}

Ivermectin is not recommended in children < 5 years because of a lack of data.¹¹ Refer young children with strongyloidiasis to a paediatrician or infectious-disease specialist.³ In remote areas where access to a specialist may be difficult, albendazole may be given.⁵ Use 200 mg once daily for 3 days if the child is < 10 kg, and 400 mg once daily for 3 days if the child is > 10 kg. Take on an empty stomach to increase intestinal absorption and repeat after 1 week.^{4,9}

Table 1: Diagnosis and treatment of hookworm and strongyloidiasis^{3,7,9}

	Hookworm	Strongyloidiasis
Diagnosis	Examine stool sample for eggs	Use serology: examining a stool sample is relatively insensitive
Treatment	Single dose of albendazole Adults and children > 10 kg: 400 mg dose (2 × 200 mg tablets) Children > 6 months and < 10 kg: 200 mg	Albendazole is second choice. Use ivermectin* except in: • children < 5 years • people with <i>Loa loa</i> ('eye worm')

* 200 micrograms/kg orally with fatty food; repeat 7–14 days later^{3,10}

Ivermectin should not be used in people who also have *Loa loa* (loiasis), as there is a risk of severe encephalopathy or death in these patients.^{3,11} Use serology to rule out *L. loa* in people from West and Central Africa (where it is endemic) or in people who report episodic subcutaneous swellings or an 'eye-worm'.³ Refer people with loiasis to an infectious-disease specialist.³

Safety

Albendazole should not be used in pregnancy or in children aged < 6 months.^{9,12} The manufacturer recommends discontinuing breastfeeding during, and for 5 days after, treatment.¹²

The most common adverse effect is abdominal pain, reported by 1% of trial participants. Other less common side effects include diarrhoea, nausea, headache, dizziness and skin rashes.^{9,12}

Federal government assistance for refugee health assessments

Medicare Benefits Schedule (MBS) item numbers 714 and 716 reimburse general practitioners who perform refugee and humanitarian entrant health assessments within 12 months of the patient's arrival in Australia.

Refugee health assessments should always be undertaken with an appropriate interpreter, preferably someone who is not known to the patient personally.³ The Telephone Interpreting Service (TIS) is available free of charge to general practitioners who provide a Medicare service to non-English speaking permanent residents or Australian citizens. Call the TIS Doctors' Priority Line (1300 131 450) to access this service.¹³

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Postmarketing reports of pancreatitis with sitagliptin products (Janumet, Januvia)

Cases of acute pancreatitis have been reported with sitagliptin (Januvia) and sitagliptin with metformin (Janumet).¹ Health professionals should be vigilant for signs and symptoms of pancreatitis during treatment and should use sitagliptin products cautiously in people with a history of pancreatitis.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Sitagliptin was first listed on the PBS in 2008, followed by sitagliptin with metformin in 2009. For more information about sitagliptin, see the *NPS RADAR* review 'Sitagliptin (Januvia) for type 2 diabetes' and In Brief item 'Sitagliptin with metformin (Janumet) fixed dose combination tablets PBS listed for type 2 diabetes mellitus'.

Pancreatitis is a possible adverse effect, but a causal association has not been confirmed

Between October 2006 and February 2009 the US Food and Drug Administration (FDA) received 88 reports of acute pancreatitis in people taking sitagliptin or sitagliptin with metformin.¹ Symptoms most commonly reported in these cases were nausea, vomiting and abdominal pain.¹ Many cases were severe: 58 required hospitalisation (4 in intensive care) and 2 involved haemorrhagic or necrotising pancreatitis.¹

In some reports the onset of pancreatitis was soon after starting sitagliptin or sitagliptin with metformin. Nineteen cases were within a month of starting treatment, and more than half of all cases resolved when treatment was stopped.¹

A causative relationship between sitagliptin and pancreatitis has not been established. Diabetes itself is a risk factor for pancreatitis. Other risk factors such as hypercholesterolaemia, hypertriglyceridaemia and obesity were also present in 51% of the US cases.¹ In clinical trials, the incidence of pancreatitis did not differ significantly between the sitagliptin (0.1%) and non-exposed groups (0%)², although the data do not rule out a rare adverse effect.

In September 2009 the FDA issued a warning to health professionals about the reports of pancreatitis, and accordingly updated the US prescribing information in December 2009.^{3,4} The Australian product information for products containing sitagliptin was updated earlier that year to include pancreatitis as a postmarketing adverse event.^{5,6}

Monitor and warn about signs and symptoms, particularly in people with risk factors

Be vigilant for the onset of persistent severe abdominal pain (sometimes radiating to the back), nausea, vomiting and/or anorexia in patients taking sitagliptin or sitagliptin with metformin.¹ Advise them to promptly report any signs and symptoms, especially if they have any additional risk factors for pancreatitis.¹

Use cautiously and closely monitor treatment in people with a history of pancreatitis.¹ Sitagliptin has not been studied in these people.¹ It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis with sitagliptin or sitagliptin with metformin.¹

If pancreatitis is suspected, stop treatment and investigate (e.g. with a serum amylase test).¹

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Authority listing for terbinafine extended to children and adolescents

The authority listing for terbinafine 250 mg tablets was extended on 1 March 2010. Any child or adolescent (< 18 years) may now receive treatment for a dermatophyte infection that has not responded to topical treatment and oral griseofulvin. Similarly, the streamlined authority listing for terbinafine 1% cream now includes the treatment of fungal or yeast infections in this age group.¹ These authority listings were previously restricted to Aboriginal and Torres Strait Islander people only.²

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the extended listings on the basis of clinical need for children and adolescents.¹ The TGA-approved product information does not recommend terbinafine tablets for children or adolescents, and the cream is not recommended for children < 12 years.^{3,4} However, there are some small trials to support use in children and adolescents^{5–7} and paediatric oral dose recommendations are available (see Box 1).^{5,8} Terbinafine oral granules* are indicated for people > 4 years in the US (with slightly higher mg/kg dose recommendations).⁹

Prescribe terbinafine tablets only if terbinafine cream and oral griseofulvin have not treated the fungal infection: if > 6 weeks of terbinafine tablets are required, monitor blood count and liver enzymes.¹⁰ Oral terbinafine is associated with rare but serious adverse effects (e.g. blood dyscrasias, liver failure).^{3,11–13} The US FDA found that skin reactions were the most often reported postmarketing adverse event for terbinafine for children.¹⁴

Box 1: Paediatric dose recommendations for terbinafine tablets†

Weight (kilogram)	Daily dose (mg)
< 20	62.5
20–40	125
> 40	250

† 250 mg scored tablets are the only strength available in Australia, so doses for children < 40 kg require tablets to be broken.

* Not available in Australia.

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Extended PBS listings for zoledronic acid 5mg (Aclasta)

From 1 April 2010, zoledronic acid 5 mg (Aclasta) can be prescribed on the PBS as the sole anti-resorptive agent for:

- osteoporosis in men without hip fracture
- people with corticosteroid-induced osteoporosis
- people with symptomatic Paget's disease.^{1,2}

The authority-required listing for zoledronic acid was previously restricted to:

- women with osteoporosis and any fracture due to minimal trauma
- women aged > 70 years with a bone mineral density (BMD) T-score of ≤ -3.0
- men with a hip fracture due to minimal trauma.

(See the NPS RADAR review: 'Zoledronic acid (Aclasta) for osteoporosis' for more information.³)

No longer restricted to men with hip fracture only

The extended PBS listing for osteoporosis allows zoledronic acid to be prescribed for men with any type of minimal trauma fracture and for men aged > 70 years with a BMD T-score of ≤ -3.0 . This is similar to the listings for alendronate and risedronate — other PBS-listed bisphosphonates for osteoporosis (see Box 1).⁴

Corticosteroid-induced osteoporosis

Zoledronic acid may now be prescribed for people on long-term high-dose (≥ 3 months at ≥ 7.5 mg daily prednisolone or equivalent) corticosteroid therapy and with a BMD T-score ≤ -1.5 . Until now, risedronate was the only other PBS-listed medicine for corticosteroid-induced osteoporosis (see the *NPS RADAR* In Brief news item: 'Risedronate [Actonel and Actonel Once-a-Week] for corticosteroid-induced osteoporosis'⁵ and Box 1 for more information).⁴ The PBAC recommended extending the listing of zoledronic acid on a cost-minimisation basis — that is, similar efficacy and cost — compared with risedronate. The equi-effective doses for this comparison were zoledronic acid 5 mg once yearly and risedronate 5 mg once daily.¹

Symptomatic Paget's disease

This extended PBS listing is similar to those of alendronate, pamidronate, risedronate and tiludronate — the other PBS-listed bisphosphonates for symptomatic Paget's disease (see Box 1).⁴ The PBAC recommended this listing on a cost-minimisation basis compared with pamidronate. The equi-effective doses for this comparison were 1 infusion of zoledronic acid 5 mg once yearly and 2 infusions of pamidronate 60 mg per year.¹

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Box 1: PBS-listed bisphosphonates for osteoporosis, corticosteroid-induced osteoporosis and symptomatic Paget's disease*⁴

Generic names	Brand names	PBS listing		
		Osteoporosis	Corticosteroid-induced osteoporosis	Symptomatic Paget's disease
Alendronate sodium	Adronat, Alendrobell, Alendro Once Weekly, Fosamax Once Weekly, Fosamax Plus, Ossmax	✓		✓
Disodium etidronate [†]	Didrocal, Didronel	✓		✓
Disodium pamidronate	Aredia, Pamisol			✓
Risedronate sodium	Actonel, Actonel Once-a-month, Actonel Once-a-week, Actonel Combi, Actonel Combi D	✓	✓	✓
Tiludronate disodium	Skelid			✓
Zoledronic acid	Aclasta	✓	✓	✓

* Streamlined authority listings except for zoledronic acid (which is authority required)

[†] Restricted to osteoporosis in patients with fracture due to minimal trauma or for symptomatic Paget's disease when calcitonin has been found to be unsatisfactory due to either lack of efficacy or unacceptable side effects

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