

A step-wise approach to heart failure management

According to estimates about 300,000 Australians are affected by heart failure with about 30,000 new cases diagnosed every year.¹

In the last decade clinical trials have identified drugs, in particular ACE inhibitors and beta-blockers, which improve survival and reduce hospital admissions for heart failure due to left ventricular dysfunction. Although routinely recommended in heart failure guidelines, evidence suggests these drugs continue to be under-prescribed.^{2,3}

Recently, the National Institute of Clinical Studies identified a number of barriers to managing heart failure optimally in primary care.⁴ This *NPS News* attempts to address some of these barriers by working through a case study of a 'typical' patient with heart failure.

Dianne's story

Dianne is a 75-year old widow who has just moved to the area to be closer to her daughter. She has a history of angina, managed with sustained-release nitrates and low-dose aspirin, and osteoarthritis for which she is prescribed rofecoxib. In recent months she has been increasingly fatigued and troubled at night by feelings of breathlessness (orthopnoea). Her previous doctor diagnosed heart failure and prescribed frusemide 40 mg daily and a potassium supplement. On examination she has a raised jugular venous pulse (JVP) but no evidence of ankle oedema or basal crepitations. Her chest X-ray shows cardiomegaly.

Confirm the diagnosis

International guidelines do not recommend diagnosis on clinical grounds alone.^{1,5} Symptoms such as fatigue, oedema, and dyspnoea are non-specific and other conditions (e.g. lung disease) may present in a similar manner.⁵ Clinical signs such as elevated JVP may be absent or difficult to detect.^{5,6}

Dianne's history of ischaemic heart disease, symptoms and signs strongly suggest heart failure but an echocardiogram should be ordered to confirm the diagnosis and exclude surgically correctable causes such as aortic stenosis.

If patients with poor mobility or in remote locations have problems accessing echocardiography services⁴, an electrocardiogram (ECG) and chest X-ray may help in diagnosis. For example, heart failure is unlikely if the ECG is normal.^{5,6}

Consider drug causes

Cease rofecoxib and trial paracetamol for Dianne's osteoarthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs), including the selective COX-2 agents, can cause sodium and

water retention and decrease glomerular filtration rate. They can worsen existing heart failure^{7,8} and probably precipitate it in patients with other cardiovascular disease.⁹

Both non-selective and COX-2 selective NSAIDs can induce acute renal failure when used in combination with ACE inhibitors and diuretics.^{10,11}

Other drugs to avoid include:

- the calcium-channel blockers verapamil and diltiazem¹
- some anti-arrhythmics (e.g. quinidine, flecainide)¹
- tricyclic antidepressants¹ and some antipsychotics (e.g. thioridazine)¹²
- in moderate to severe heart failure, the new antidiabetic agents rosiglitazone and pioglitazone¹³ (see *NPS RADAR* summaries on rosiglitazone and pioglitazone at www.npsradar.org.au).

Using low-dose aspirin (up to 150 mg daily) is controversial but without clear evidence of benefit or harm, some guidelines support its use in patients with both coronary artery disease and heart failure.^{5,14}

Erratum *NPS News* 35 August 2004

In the table *Choosing an antidepressant for special patient groups*, included in *NPS News* 35, the word 'faster' should be substituted for 'slower' as shown below. A replacement table has been sent to all GPs and pharmacists.

'Pregnancy:

General issues and concerns

Prescribing Points

Withdrawal symptoms in infants are similar in all antidepressant classes. Their onset and severity depend on the drug's half-life (shorter half-life means **faster** [not 'slower'] onset and more intense symptoms).⁷

We apologise for any confusion.

Dianne's story

Despite stopping rofecoxib, Dianne's symptoms do not resolve. An echocardiogram confirms she has heart failure due to left ventricular systolic dysfunction (see box at bottom of page). A step-wise approach to managing Dianne's condition is discussed in the following sections and summarised in Figure 1, on page 5.

Start an ACE inhibitor

If baseline blood pressure, creatinine and electrolytes are in normal range, commence a low-dose ACE inhibitor (e.g. enalapril 2.5 mg daily). ACE inhibitors, if tolerated, are recommended for all patients with heart failure, whether symptoms are mild, moderate or severe.¹

A meta-analysis of over 12,000 patients with left ventricular dysfunction and/or heart failure from five large trials (three post-myocardial infarction) found that treating 100 such patients with an ACE inhibitor for two and a half years could prevent seven major events (defined as death, admission for heart failure or re-infarction).¹⁵

ACE inhibitors can also relieve symptoms in heart failure but **the primary reason to prescribe an ACE inhibitor is to reduce risk of death or hospitalisation**. For this reason, ACE inhibitors should not be adjusted according to symptoms but titrated to the doses known to improve survival in randomised controlled trials, or failing that, to the highest tolerated dose.

Start low and go slow

Some people are at higher risk of adverse events when starting treatment¹⁶:

- on high doses of potent diuretics
- with severe heart failure
- sodium < 130 mmol/L
- creatinine >150 micromol/L or
- systolic blood pressure < 100 mm Hg.

For these people, specialist advice may be needed. Most others can tolerate higher doses of ACE inhibitors as long as the following precautions are taken during titration:

- consider stopping diuretics for 24 hours; start with a low dose (Table 1) and advise patient to either sit or lie down for 2–4 hours after this initial dose^{16–18}
- double the dose at not less than two-weekly intervals, if lower doses are well tolerated⁵
- check blood pressure, renal function and serum potassium before treatment, one to two weeks after starting, at each dose increase until stable, and then at least annually.¹⁶

Table 1: Dosage recommendations for ACE inhibitors in patients with systolic heart failure¹⁷

ACE inhibitor	Starting dose	Target maintenance dose
captopril	6.25 mg twice daily	50 mg three times daily
enalapril	2.5 mg daily	10–20 mg twice daily
fosinopril	5 mg daily	20–40 mg daily
lisinopril	2.5 mg daily	20–40 mg daily
perindopril	2 mg daily	4–8 mg daily
quinapril	2.5 mg daily	20–40 mg daily
ramipril	1.25 mg daily	5–10 mg daily
trandolapril	0.5 mg daily	2–4 mg daily

[†] Doses in the lower range and slower titration may be indicated if significant renal impairment or symptomatic hypotension is present.

Systolic versus diastolic heart failure

In most patients heart failure is due to left ventricular systolic dysfunction, where the ventricle is dilated and poorly contracting (left ventricular ejection fraction < 40%).^{1,19} Ischaemic heart disease is the most common cause. Most of the evidence for the pharmacological management of heart failure relates to **systolic heart failure**, as it is now often called. To avoid confusion, systolic heart failure is simply referred to as 'heart failure' throughout this *NPS News*.

However, about a third of patients (often elderly and female) are thought to have **diastolic heart failure**.^{20,21} Obesity, hypertension and diabetes are risk factors.²¹ In diastolic heart failure, ejection fraction is normal but the ventricle is stiff, with thick walls and a small cavity.²⁰ Relaxation (diastole) and ventricular filling are abnormal. Current treatment of diastolic heart failure is less evidence-based.²⁰ Whilst many of the drugs used to treat systolic heart failure are useful in diastolic failure, management strategies vary. For example, patients with diastolic heart failure are more sensitive to the effects of diuretics, but less sensitive to beta-blockers.¹⁷

Managing ACE inhibitor adverse effects

Many GPs are reluctant to use ACE inhibitors at recommended doses because of worries regarding adverse effects such as hypotension, renal impairment, angioedema and cough.⁴ Angioedema is a reason to stop treatment immediately but, if appropriate steps are taken (see Table 2), other adverse effects can be successfully managed in most people to enable target doses to be achieved.¹⁹

Table 2: Problem solving when using ACE inhibitors in heart failure (adapted from NICE Chronic Heart Failure Guidelines, 2003)⁵

<p>Hypotension</p> <ul style="list-style-type: none"> Asymptomatic low blood pressure does not usually require any change in therapy. If no symptoms of congestion, consider reducing diuretic dose. If dizziness, light-headedness and/or confusion and low blood pressure, consider discontinuing nitrates or other vasodilators. If these measures do not work, seek specialist advice. 	<p>Worsening renal function</p> <ul style="list-style-type: none"> Some rise in urea, creatinine and potassium is expected after commencing an ACE inhibitor; if the increase is small and asymptomatic, no action is necessary. A rise in creatinine of up to 50% above baseline, or to 200 micromol/L, whichever is the smaller, is acceptable. An increase in potassium to ≤ 5.9 mmol/L is acceptable. If urea, creatinine or potassium do rise excessively, consider stopping non-essential vasodilators, potassium supplements/retaining agents (e.g. amiloride) and, if no signs of congestion, reducing the dose of diuretic. If excessive rises in creatinine or potassium persist, despite adjustment of concomitant medications, halve the dose of ACE inhibitor and re-check blood chemistry; if there is still an unsatisfactory response seek specialist advice.[‡] If potassium ≥ 6.0 mmol/L or creatinine increases by $> 100\%$ or to > 350 micromol/L stop the ACE inhibitor and seek specialist advice. <p>[‡] A persistent excessive rise in creatinine may indicate bilateral renal artery stenosis.</p>
<p>Cough</p> <ul style="list-style-type: none"> Cough is common in patients with heart failure. Pulmonary congestion should be excluded if a new or worsening cough develops. ACE inhibitor cough rarely requires discontinuing treatment. If the patient develops a troublesome dry cough that interferes with sleep and is likely to be caused by an ACE inhibitor, consider substituting an angiotensin II receptor antagonist. 	

Diuretic monotherapy is not appropriate

Dianne's heart failure should not be managed by diuretic therapy alone. **There is no evidence that thiazide or loop diuretics reduce mortality in heart failure.**¹⁹ However, most people are likely to need a diuretic to control fluid symptoms—usually a more potent loop diuretic, such as frusemide. Adjust dose according to fluid symptoms.

Monitor renal function and electrolytes; patients also taking ACE inhibitors (or angiotensin II receptor antagonists) may not need potassium replacement.¹⁸



Heart Foundation



**NATIONAL INSTITUTE
OF CLINICAL STUDIES**



National Prescribing Service Limited

These NPS materials form part of a joint program with the National Heart Foundation of Australia and the National Institute of Clinical Studies to improve the management of heart failure.

Beta-blockers are recommended, not contraindicated

Dianne's story

Dianne's enalapril has been successfully titrated to 10 mg twice daily but she remains mildly symptomatic. As she does not have airways disease, beta-blockers are indicated.

Large, well-conducted studies have shown that selected beta-blockers improve survival and decrease hospitalisations in stable symptomatic heart failure. Overall, beta-blockers reduce the annual mortality rate by an absolute 4.5% (translating to a number-needed-to-treat of 22 to prevent one death in a year). This survival benefit is **in addition** to the benefits gained with ACE inhibitors.¹⁴

Beta-blockers can have potential complications such as initial worsening of heart failure, hypotension and bradycardia. Initiation and up-titration is therefore best undertaken in consultation with a specialist.¹⁷

To minimise complications:

- start with extremely low doses¹⁷
- increase the dose very gradually, at not less than two-weekly intervals, and only if lower doses have been well tolerated^{5,17}

- monitor heart rate, blood pressure and clinical status frequently, with daily weighing^{5,17}
- adjust the dose of other medications such as diuretics¹⁷
- refer patients with very severe or poorly controlled heart failure to a specialist.¹⁷

Beta-blockers improve survival in diabetic patients with heart failure^{19,22} and may be used with close monitoring of glucose and lipids.

For more information see *NPS RADAR* summaries on metoprolol succinate controlled-release and carvedilol titration pack at www.npsradar.org.au.

Table 3: Dosing regimens of beta-blockers approved to treat heart failure in Australia^{17,23}

Beta-blocker	Starting dose	Titration regimen	Target dose
Bisoprolol	1.25 mg once daily	Double dose every 2–4 weeks if patient is stable	10 mg once daily
Carvedilol	3.125 mg twice daily	Double dose every 2–4 weeks if patient is stable	25 mg twice daily
Metoprolol succinate extended-release	23.75 mg once daily If moderate–severe heart failure: half tablet daily for 1 week then 1 tablet daily for 1 week	Double dose every 2–4 weeks if patient is stable	190 mg once daily

Good communication is the key

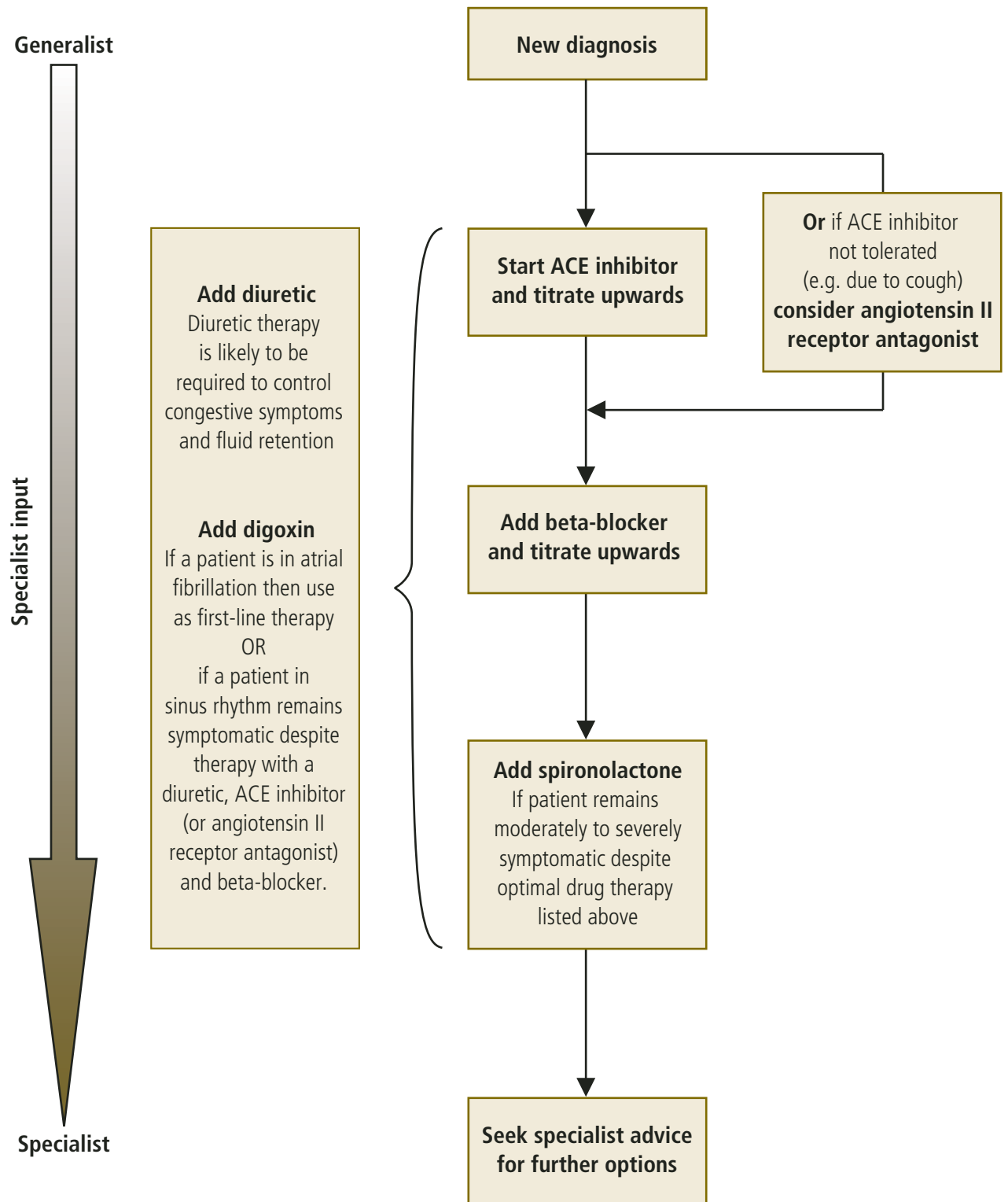
Successful management of heart failure depends on good communication between all parties—patient, GP, specialist and other health professionals.

Dianne needs to know about lifestyle changes such as salt and fluid restriction, potential side-effects of her medicines, the need to report signs of deterioration (e.g. weight gain, dyspnoea) and the importance of adherence to therapy.¹ Encourage her active involvement: for example,

she can be instructed to adjust her diuretic dosage in response to changes in body weight.^{1,19}

Written information is likely to help. The National Institute of Clinical Studies has identified four high quality patient publications on heart failure, available at the **Heart Failure Resources Directory** www.nicsl.com.au/projects_projects_detail.aspx?view=15&subpage=19.

Figure 1 – Algorithm for pharmacological management of heart failure due to left ventricular systolic dysfunction (adapted from the NICE Chronic Heart Failure Guidelines, 2003)⁵



Other evidence-based options

These may be needed if symptom control or ACE inhibitor intolerance is a problem.

Spironolactone for severe heart failure

Low-dose spironolactone is an option in patients with moderate to severe heart failure. When added to ACE inhibitor and diuretic therapy, spironolactone 25 mg daily reduced the relative risk of death by 30% (absolute risk reduction 11%) over two years in patients with severe heart failure.²⁴

When taken with ACE inhibitors, spironolactone may cause life-threatening hyperkalaemia, particularly in elderly patients with renal impairment.^{25,26} Careful monitoring is essential.

Angiotensin II receptor antagonists for ACE inhibitor intolerance⁵

Large outcome trials with valsartan and candesartan confirm that angiotensin II receptor antagonists can improve prognosis in heart failure.^{27,28} Angiotensin II receptor antagonists are therefore suitable for people unable to tolerate ACE inhibitors due to adverse effects such as cough.^{1,5,17}

Combined ACE inhibitor–angiotensin II receptor antagonist treatment can reduce end-points such as hospitalisations for heart failure^{28,29} when compared with ACE inhibitors alone but also appears more likely to produce adverse events.^{29,30} It is best reserved for specialist management at this stage.

⁵ Angiotensin II receptor antagonists are not currently listed on the PBS for the treatment of heart failure.

Digoxin for symptom relief

Digoxin reduces hospitalisations but not mortality in heart failure.³¹ There are two indications for its use^{1,5,17}:

- In patients with **heart failure and atrial fibrillation**, to control ventricular rate at rest.
- A limited second-line role in **heart failure and sinus rhythm**, to relieve symptoms not controlled with diuretics, ACE inhibitors and beta-blockers. It should not be preferred to treatments which improve survival.^{5,19}

Adjust digoxin dosage according to symptoms. Plasma-digoxin concentrations may help confirm toxicity (unlikely below 0.8 micrograms/L)¹⁸ but have a weak relationship to therapeutic effect.^{5,19} Check renal function and potassium levels before starting treatment.

Reviewers

Dr James Best, General Practitioner
A/Prof Nick Buckley, Clinical Pharmacologist, The Canberra Hospital
Ms Jan Donovan, Consumer
Dr John Dowden, Australian Prescriber
Ms Simone Rossi, Australian Medicines Handbook
Prof John Murtagh, Dept of General Practice, Monash University, Melbourne
Ms Susan Parker, Australian Self-Medication Industry

Any correspondence regarding content should be directed to the NPS. Declarations of interest have been sought from all reviewers.

Expert reviewer:

Dr Jo-Dee Lattimore
Director, Heart Failure Clinic
Royal Prince Alfred Hospital, Sydney

References:

1. National Heart Foundation of Australia and The Cardiac Society of Australia and New Zealand. Guidelines on the contemporary management of the patient with chronic heart failure in Australia; 2002. new.heartfoundation.com.au/downloads/cont.management.pdf. Accessed August 2004.
2. Krum H, et al. *Med J Aust* 2001; 174:439–44.
3. AIHW GPSCU. SAND abstract No. 38 from the BEACH program 2002–03: Prevalence of chronic heart failure, management and control. Sydney: GPSCU and AIHW; 2003.
4. Phillips SM, et al. *Med J Aust* 2004;181:78–81.
5. The National Collaborating Centre for Chronic Conditions. NICE Guideline No.5, Chronic Heart Failure: National clinical guideline for diagnosis and management in primary and secondary care; 2003.
6. NICS. The diagnosis and recognition of congestive cardiac failure. Prepared by Centre for Evidence Based Practice at the University of Queensland. Melbourne: NICS; 2002.
7. Feenstra J, et al. *Arch Intern Med* 2002;162:265–70.
8. Mamdani M, et al. *Lancet* 2004; 363:1751–6.
9. Page J, Henry D. *Arch Intern Med* 2000;160:777–84.
10. Thomas MC. *Med J Aust* 2000; 172:184–5.
11. Boyd IW, et al. *Med J Aust* 2000; 173:274.
12. MIMS Annual 2003.
13. Nesto RW, et al. *Circulation* 2003;108:2941–8.
14. National Heart Foundation of New Zealand. A guideline for the management of heart failure: health professionals guide. Auckland: National Heart Foundation of New Zealand; 2001. www.nzgg.org.nz/guidelines/0026/CHF_Guide.pdf. Accessed August 2004.
15. Flather MD, et al. *Lancet* 2000; 355:1575–81.
16. PRODIGY Guidance – Heart failure. Revised June 2004. Available at [www.prodigy.nhs.uk/guidance.asp?gt=Heart failure](http://www.prodigy.nhs.uk/guidance.asp?gt=Heart%20failure).
17. Therapeutic Guidelines: Cardiovascular. Version 4, 2003.
18. Australian Medicines Handbook 2004.
19. American College of Cardiology/American Heart Association – Guidelines for the evaluation and management of chronic heart failure in the adult: American College of Cardiology and American Heart Association, Inc; 2001.
20. Vasan RS. *BMJ* 2003;327:1181–2.
21. Jessup M, Brozena S. *N Engl J Med* 2003;348:2007–18.
22. Haas SJ, et al. *Am Heart J* 2003;146:848–53.
23. Toprol-XL Product Information. AstraZeneca Pty Ltd. December 2003.
24. Pitt B, et al. *N Engl J Med* 1999; 341:709–17.
25. Wrenger E, et al. *BMJ* 2003; 327:147–9.
26. Juurlink DN, et al. *N Engl J Med* 2004;351:543–51.
27. Granger CB, et al. *Lancet* 2003; 362:772–76.
28. Cohn JN, et al. *N Engl J Med* 2001; 345:1667–75.
29. McMurray JJ, et al. *Lancet* 2003; 362:767–71.
30. Pfeffer MA, et al. *N Engl J Med* 2003;349:1893–1906.
31. Digitalis Investigation Group. *N Engl J Med* 1997;336:525–33.

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 individual clinical circumstances of each patient.



National Prescribing Service Limited

Our goal To improve health outcomes for Australians through prescribing that is: **s safe s effective s cost-effective**
Our programs To enable prescribers to make the best prescribing decisions for their patients, the NPS provides:
s information s education s support s resources

Level 7 / 418A Elizabeth Street Surry Hills NSW 2010

Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | net: <http://www.nps.org.au>