

Ramipril (Tritace) titration pack

Summary

PBS listing:	New listing. Unrestricted
Reason for listing:	More efficient use of tablets for patients to be titrated to ramipril 10 mg daily for cardiovascular risk reduction.
Place in therapy:	To aid titration to the target daily dose of 10 mg for patients at increased cardiovascular risk. Should not be used for dose titration of ramipril for essential hypertension, heart failure, proteinuria or for patients who require individualised dose titration.
Safety issues:	Check blood pressure, renal function and electrolytes before starting therapy and review one week after starting and at each dose increment. Not suitable for people at risk of hypotension, acute renal failure, hyperkalaemia or those with hepatic impairment.
Dosing issues:	Lower starting doses and individualised dose titration may be required in people at risk of hypotension, renal failure or hyperkalaemia, in the elderly and in people with impaired hepatic or renal function.

PBS Listing

New listing. Unrestricted.

Reason for PBS listing

The PBAC considered the titration pack presentation was a more efficient use of tablets for titrating to a dose of ramipril 10 mg daily for cardiovascular risk reduction.¹

Place in therapy

The titration pack is intended to aid titration to the target ramipril dose of 10 mg daily for the reduction of cardiovascular risk in patients aged 55 years or more who have clinical evidence of coronary artery disease, stroke, peripheral vascular disease, or who have diabetes and one other cardiovascular risk factor.² This indication for ramipril is based on the Heart Outcomes Prevention Evaluation (HOPE) study, which used the same titration regimen (2.5 mg/day for one week, 5 mg/day for 3 weeks, then 10 mg/day).³

ACE inhibitors can cause severe hypotension, acute renal failure and hyperkalaemia. Blood pressure, renal function and electrolytes must be monitored during dose escalation so that adverse events are detected promptly (see 'Minimising the risks' under *Safety Issues: Contra-indications and precautions*). Advise patients of the importance of returning regularly for monitoring.

The titration pack should not be used in essential hypertension, where the dose must be adjusted according to antihypertensive effects, nor is it suitable for dose titration in heart failure or proteinuria.

Safety issues

Increasing the dose of ramipril without intervening medical supervision may place some patients at risk of severe hypotension, acute renal failure or hyperkalaemia.

Contra-indications and precautions

Severe hypotension, acute renal failure and hyperkalaemia are possible adverse effects of ACE inhibitors. All patients must have blood pressure, renal function and electrolytes checked before starting ramipril and reviewed regularly during dose escalation.

Consider factors that may place patients at risk of serious adverse effects. Patients with any of the risk factors listed below should be initiated on a dose of 1.25 mg/day and closely monitored.

Although the titration pack uses the same regimen as HOPE, patients in the study were not necessarily representative of those seen in clinical practice; many of those at risk of serious adverse events were ineligible, or were excluded because of adverse events during the run-in phase with ramipril 2.5 mg daily. The rate of adverse events during dose escalation in HOPE was not reported. However, in a recent study with another ACE inhibitor, problems (including hyperkalaemia, elevated serum creatinine and hypotension) arose during dose escalation, highlighting the need for careful monitoring in this period.⁴

Risk factors⁵

- Dehydration or high diuretic dose
- Serum sodium < 130 mmol/L
- Elderly (> 75 years)
- Heart failure
- Hyperkalaemia
- Severe or complicated hypertension
- Valvular stenosis
- Existing renal impairment (creatinine clearance < 50 mL/min)
- Renal artery stenosis (ACE inhibitors are contra-indicated in either bilateral or unilateral with a single functioning kidney)
- Low pre-treatment blood pressure (systolic blood pressure < 100 mmHg)
- Concomitant use of NSAIDs (including COX-2 selective NSAIDs), potassium-sparing diuretics or potassium supplements

Minimising the risks

Measure blood pressure, renal function and electrolytes

- before initiating therapy,
- approximately one week after initiating therapy,
- after each increase in dose, and
- at 6–12 month intervals, once stable.

Before starting ACE inhibitor therapy

- correct dehydration.
- consider withholding diuretics for at least 24 hours or reduce the dose for several days for those taking high diuretic doses.
- cease potassium-sparing diuretics and potassium supplements.
- cease NSAIDs and COX-2 selective NSAIDs where possible.

The titration pack is unsuitable for patients with hepatic impairment, who should not receive ramipril doses above 2.5 mg/day.²

Dosing issues

Lower starting doses and individualised dose titration may be required in people at risk of hypotension, renal failure or hyperkalaemia, in the elderly, and in people with impaired hepatic or renal function (see *Safety Issues*).

Consumer information

Instruct the patient to

- take their first dose in the evening just before going to bed to minimise first-dose hypotension.
- get up slowly when standing up or getting out of bed.
- return for monitoring one week after starting ramipril and each time the dose is increased.
- report unwanted side-effects as the dose increases.
- ask the pharmacist for the Tritace Consumer Medicine Information (CMI).

Advise patients of the importance of lifestyle changes in reducing overall cardiovascular risk. Information about lifestyle changes for patients is available from the Heart Foundation's national telephone information service, *Heartline* (Ph 1300 36 27 87) or online (www.heartfoundation.com.au).

National Prescribing Service has developed a 'non-prescription' pad designed to assist doctors to prescribe appropriate lifestyle changes to reduce cardiovascular risk. The tear-off 'scripts' in the pad include practical suggestions for dietary changes that can be tailored to suit each patient's needs. Information is also provided to assist doctors to recommend other changes to reduce cardiovascular risk. Pads are available free of charge from NPS (email info@nps.org.au or phone (02) 8217 8700).

References

1. Department of Health & Ageing. June 2003 PBAC outcomes – positive recommendations. (<http://www.health.gov.au/pbs/general/listing/pbacrec/jun03/positive.htm#ramipr> Accessed 6 August 2003).
2. Aventis Pharma Pty Ltd. Tritace Product Information. 13 January 2003.
3. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. *N Engl J Med* 2000;342:145–53.
4. The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators. *Lancet* 2003;362:782–8.
5. National Prescribing Service. Management of Heart Failure. NPS Practice Visits Program, June 2000.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each point.

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