NPS RADAR
Rational Assessment of Drugs and Research

Moxifloxacin (Avelox) tablets for community-acquired pneumonia
(moks-i-FLOX-asin)

Summary

PBS listing:	**Authority required.** Radiologically confirmed, community-acquired pneumonia in patients greater than 12 years old with a history of immediate hypersensitivity to penicillin.
Reason for listing:	The PBAC recommended extending the listing to include this new patient group being treated for community-acquired pneumonia outside the hospital setting on the basis of acceptable cost-effectiveness against the likely alternative of hospitalising such patients.
Place in therapy:	Current Australian recommendations for the treatment of community-acquired pneumonia in ambulatory care are: Amoxycillin plus *either* doxycycline *or* roxithromycin Moxifloxacin should be reserved for patients with immediate penicillin hypersensitivity (as defined by urticaria, angioedema, bronchospasm or anaphylaxis within one hour of drug administration).
Safety issues:	Moxifloxacin has been associated with QT prolongation, can cause tendon rupture, and may damage cartilage in children.
Dosing issues:	Antacids or other preparations containing magnesium, aluminium, calcium, zinc or iron can impair moxifloxacin absorption; separate moxifloxacin administration from ingestion of such preparations by at least two hours.

PBS Listing

Moxifloxacin 400 mg tablets
Authority required.
Radiologically confirmed, community-acquired pneumonia in patients greater than 12 years old with a history of immediate hypersensitivity to penicillin (as defined by urticaria, angioedema, bronchospasm or anaphylaxis within one hour of drug administration).

Reason for PBS listing

This extends the current listing for oral moxifloxacin to include a new patient group being treated for community-acquired pneumonia outside the hospital setting.

The PBAC recommended the extension of the listing on the basis of acceptable cost-effectiveness against the likely alternative of hospitalising such penicillin-allergic patients in the absence of any other regimen recommended in the 2003 edition of *Therapeutic Guidelines: Antibiotic*.[1]

Place in therapy

Current Australian recommendations[2] for the treatment of community-acquired pneumonia in ambulatory care are:

Amoxycillin plus *either* doxycycline *or* roxithromycin

Moxifloxacin should be reserved for patients with immediate penicillin hypersensitivity (as defined by urticaria, angioedema, bronchospasm or anaphylaxis occurring within one hour of drug administration).[2]

Grading the severity of community-acquired pneumonia

A new patient classification system—the Pneumonia Severity Index (PSI)—stratifies patients according to their risk of mortality.[3] Those considered at low risk can be treated in an outpatient setting. See T*herapeutic Guidelines: Antibiotic 2003* for a complete explanation and treatment algorithm.

Amoxycillin plus either doxycycline or roxithromycin are first choice

Streptococcus pneumoniae (pneumococcus) is the most common cause of community-acquired pneumonia. Amoxycillin remains effective against most strains of *S. pneumoniae* and is the drug of first choice.[4]

Doxycycline or roxithromycin are used in combination with amoxycillin as they are effective against other potential pathogens not covered by amoxycillin.[4]

Reserve moxifloxacin for patients with immediate penicillin hypersensitivity

Moxifloxacin has no proven clinical advantages over existing antibiotic therapies for community-acquired pneumonia but may be used for patients with a history of immediate penicillin hypersensitivity (as defined by urticaria, angioedema, bronchospasm or anaphylaxis occurring within one hour of drug administration). Overuse of the newer quinolone antibiotics could generate resistance to what are valuable reserve agents.[4] Judicious use may extend the clinical use of these agents.[5]

Safety issues

Moxifloxacin has been associated with QT prolongation and, in common with all quinolones, can cause tendon rupture and may damage cartilage in children.

Adverse Drug Reactions

Moxifloxacin has been associated with QT prolongation which has the potential to cause arrhythmias. It should not be given to patients with a prolonged QT_c interval, with hypokalaemia, or be combined with drugs known to prolong the QT_c interval (such as erythromycin, clarithromycin, cisapride, anti-arrhythmics, tricyclic antidepressants, and antipsychotics).

ADRAC has issued a reminder to prescribers that tendon disorders are a class effect of quinolones. There have been 112 Australian cases of tendon disorders with the quinolones reported to ADRAC, including 30 cases of tendon rupture; almost all have involved the Achilles tendon. Increasing age and concomitant corticosteroids are established risk factors.[6] Cease moxifloxacin at first sign of tendon pain or inflammation.[5]

Caution use in children

Quinolones cause arthropathy in the weight-bearing joints of immature animals. Although damage to growing cartilage has not been demonstrated in humans, quinolones are not recommended for use in children and adolescents except for severe infections where benefit outweighs the risk of arthropathy.[5]

The PBS restriction pertains to patients aged greater than 12 years. Alternative antibiotic regimens are advised in adolescents.

Dosing issues

Separate, by at least two hours, administration of moxifloxacin tablets from ingestion of antacids or other preparations containing magnesium, aluminium, calcium, zinc or iron.[5] Moxifloxacin absorption can be impaired by such preparations, resulting in lower than desired plasma-moxifloxacin concentrations and potential treatment failure.

Consumer information

Advise the patient to[5]

- be alert for pain or discomfort in the Achilles tendon or calf and inform their doctor if this occurs
- tell the doctor if they have any palpitations or fainting spells
- ask the pharmacist for the Avelox Consumer Medicine Information (CMI).

References

1. Department of Health & Ageing. June 2003 PBAC outcomes – positive recommendations. (http://www.health.gov.au/pbs/general/listing/pbacrec/jun03/positive.htm#moxif Accessed 6 August 2003).
2. Therapeutic Guidelines: Antibiotic Version 12. North Melbourne: Therapeutic Guidelines Ltd; 2003.
3. Fine MJ, et al. N Engl J Med 1997;336:243–50.
4. Johnson PDR, et al. Med J Aust 2002;176:341–7.
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6. Australian Adverse Drug Reactions Bulletin 2002:21(4) (http://www.health.gov.au/tga/adr/aadrb/aadr0212.htm#3 Accessed 6 August 2003).

Prepared October 2003

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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 factors[5]

- 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.
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