

Olmesartan medoxomil (Olmotec) monotherapy or in combination with hydrochlorothiazide (Olmotec Plus) for hypertension

(OL-meh-SAR-tan meh-DOX-o-mil)

Summary

- Olmesartan reduces blood pressure to a similar extent as other angiotensin II-receptor antagonists. As there is no long-term clinical outcome evidence or long-term safety data for olmesartan, its use should be considered after that of other drugs in the class, which have more evidence and experience of use.
- There is no clinical trial evidence to show whether olmesartan is beneficial for any coexisting conditions.
- Olmesartan/hydrochlorothiazide in combination reduces systolic and diastolic blood pressure more effectively than either component as monotherapy.
- Consider olmesartan/hydrochlorothiazide combination therapy if blood pressure is not adequately controlled with either hydrochlorothiazide or olmesartan 20 mg/day. Olmesartan 40 mg/day reduces blood pressure only marginally more than 20 mg/day.
- The combined formulation should not be used to initiate therapy for hypertension. When combination therapy is needed, establish the effective dose of each component as individual medications before changing to the combined formulation.
- Based on short-term studies, the tolerability profile of olmesartan appears to be similar to that of other angiotensin II-receptor antagonists. Dizziness was more frequently reported by olmesartan-treated patients, compared with placebo.
- Olmesartan 10 mg tablets are not available in Australia. Choose an alternative antihypertensive for patients who have a lower than usual dose requirement (e.g. elderly patients and patients with mild to moderate renal impairment).
- The concomitant use of olmesartan, diuretics (including hydrochlorothiazide) and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk of acute renal failure. Combination therapy with these medications should be avoided or used with extreme caution.
- Ensure that patients return to have their renal function, and potassium and other electrolyte levels checked 1–2 weeks after starting treatment and at each dose change.

PBS listing

Unrestricted benefit

Olmesartan medoxomil (Olmotec) is listed on the Pharmaceutical Benefits Scheme (PBS) as an unrestricted benefit¹, as are other angiotensin II-receptor antagonists.

Restricted benefit

Olmesartan with hydrochlorothiazide (Olmotec Plus 20/12.5 mg, 40/12.5 mg and 40/25 mg combinations) is restricted to patients with hypertension who are not adequately controlled with either hydrochlorothiazide or olmesartan monotherapy.²

Reason for PBS listing

The PBAC recommended olmesartan for listing on the basis that it has similar efficacy to that of irbesartan at a similar or lower cost (i.e. cost minimisation). The equi-effective doses were taken to be olmesartan 1 mg and irbesartan 7.5 mg.³

The PBAC recommended olmesartan/hydrochlorothiazide for listing on the basis of cost minimisation compared with the corresponding strengths of the olmesartan and hydrochlorothiazide components given concomitantly.

Place in therapy

Olmesartan is an angiotensin II-receptor antagonist that inhibits vasoconstriction by selectively inhibiting the binding of angiotensin II to angiotensin II subtype 1 (AT₁) receptors in vascular smooth muscle.⁴ Angiotensin II-receptor antagonists have similar blood pressure-lowering effects to those of most other antihypertensive classes.⁵ These medications may be considered for treating uncomplicated hypertension, as monotherapy in patients with relevant comorbidities or intolerances (e.g. diabetic nephropathy or angiotensin-converting enzyme [ACE] inhibitor-induced cough) or as adjunctive therapy in patients whose blood pressure is inadequately controlled by thiazide diuretics. There are no published clinical trials that have investigated whether olmesartan is beneficial for specific coexisting conditions (e.g. diabetic nephropathy).

Olmesartan reduces blood pressure to a similar extent as other angiotensin II-receptor antagonists but has no clinical outcome evidence

In one randomised controlled trial, olmesartan was equally effective as losartan and valsartan in reducing diastolic and systolic blood pressure and in the proportion of patients who reached blood pressure targets, after 12 weeks of treatment.⁶ Although some short-term trials indicate a faster onset of action and a higher proportion of patients reaching 24-hour blood pressure goals with olmesartan, compared with other angiotensin II-receptor antagonists^{6–10}, it is not clear whether this translates into a clinically meaningful difference between olmesartan and the rest of the class.

To date there have been no long-term studies to assess any sustained effects or clinical outcome benefits of

olmesartan treatment. Other angiotensin II-receptor antagonists are available that lower blood pressure to a similar extent and have clinical outcome data; use of olmesartan should be considered after these. For patients with coexisting conditions, use angiotensin II-receptor antagonists that have demonstrated a benefit for the particular condition (e.g. candesartan in patients with heart failure¹¹).

Hydrochlorothiazide is a first-line antihypertensive

Hydrochlorothiazide is one of the first-line choices for uncomplicated hypertension.^{12,13} Hydrochlorothiazide is commonly used in combination with other antihypertensives when more than one medication is needed.¹⁴

High doses of thiazide diuretics (equivalent to 50 mg hydrochlorothiazide) are associated with metabolic adverse effects (e.g. glucose intolerance, increased uric acid and plasma cholesterol). However, doses up to 25 mg/day are generally considered to have minimal metabolic side effects.¹⁵

Although Olmetec Plus is the only available angiotensin II-receptor antagonist/hydrochlorothiazide combination that has a 25 mg hydrochlorothiazide component, patients should not be switched from other angiotensin II-receptor antagonists or angiotensin II-receptor antagonist/hydrochlorothiazide combinations on this basis alone.


Olmesartan/hydrochlorothiazide as a fixed-dose combination therapy

The fixed-dose combination of olmesartan and hydrochlorothiazide is an option for patients who do not achieve adequate blood pressure lowering with hydrochlorothiazide or olmesartan alone, and whose doses of the individual agents in combination are stable. Clinical studies suggest that the combination reduces systolic and diastolic blood pressure further than either component as monotherapy.^{16,17} The combination of olmesartan 40 mg and hydrochlorothiazide 25 mg was quantitatively most effective, although the difference between this and the olmesartan 20 mg/hydrochlorothiazide 25 mg combination was marginal.¹⁶ The higher olmesartan dose is unlikely to result in much greater blood pressure lowering (see Table 1).

Table 1: Placebo-adjusted changes in sitting systolic and diastolic pressure (mmHg)^{16,18}

Hydrochlorothiazide dose	Olmesartan dose			
	Placebo	10 mg*	20 mg	40 mg
Placebo	—	7/5	12/5	13/7
12.5 mg	5/1	17/8	17/8	16/10
25 mg	14/5	19/11	22/11	24/14

* Olmesartan 10 mg is not available in Australia

The usual considerations that apply to combination preparations remain important.¹⁹ Do not initiate olmesartan or hydrochlorothiazide therapy with the fixed-dose combination. Establish the effective dose of each using the individual medications, before prescribing the appropriate combination. [www](#) 

Safety issues

In short-term studies the safety profile of olmesartan was similar to that of other angiotensin II-receptor antagonists.^{6,8} The incidence of adverse effects, unrelated to the mechanisms of action of olmesartan and hydrochlorothiazide, was generally similar between olmesartan or olmesartan/hydrochlorothiazide and placebo in clinical studies up to 2 years.^{16,18,20,21} Dizziness, however, seems to be more frequent in olmesartan-treated patients than with placebo.^{16,18} In clinical trials, minor increases in urea and creatinine concentrations occurred more frequently with the combination.^{16,18} Otherwise the addition of hydrochlorothiazide to olmesartan did not increase the number of adverse effects.^{16,18} Olmesartan and olmesartan/hydrochlorothiazide have been available in the USA since 2002, with no significant safety issues identified to date.

Monitor patients for renal impairment, hypotension and hyperkalaemia. Angioedema and cough seem to be rare with olmesartan.^{22,23} However, as a precaution, consider medications from another antihypertensive class in patients with a history of ACE inhibitor-induced angioedema.¹¹

Olmesartan is contraindicated during pregnancy (Category D), as it can cause foetal or neonatal morbidity and death.⁴

No significant drug interactions with olmesartan are described. However, the concomitant use of angiotensin II-receptor antagonists or ACE inhibitors, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk of acute renal failure.^{18,24} Avoid using these classes of medications concomitantly, particularly in elderly patients or those with pre-existing renal impairment.^{25,26}


Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Dosing issues

Start olmesartan at 20 mg/day. Although the antihypertensive effect of olmesartan is dose dependent^{16,21}, the recommended dose is 20 mg/day. Olmesartan 40 mg/day only marginally increases the blood pressure-lowering response^{16,21,23} (see Table 1).

When olmesartan has been added to hydrochlorothiazide and the effective doses are determined and stable, consider changing to the combined preparation at the same dose. An olmesartan 20 mg / hydrochlorothiazide 25 mg fixed-dose combination tablet is not available (see Table 2), and separate tablets must be used if this dose combination is needed.

In elderly patients and patients with mild to moderate renal impairment, consider an alternative antihypertensive. The 10 mg dose, which is recommended as the starting dose of olmesartan in these patients^{4,18}, is not available in Australia.

[www](#)  Refer to this review at www.npsradar.org.au for assessing the usefulness of the fixed-dose combination preparation.

Information for patients

Advise patients:

- to take olmesartan or olmesartan/hydrochlorothiazide at about the same time each day (this assists adherence)
- which of their existing medicines are being replaced by olmesartan or olmesartan/hydrochlorothiazide combination tablets and to discard the unneeded medications
- to return to have their renal function, potassium and other electrolytes checked 1–2 weeks after starting treatment and at each dose change

- to tell their doctor or pharmacist that they are taking olmesartan/hydrochlorothiazide if they also need anti-inflammatory painkillers (i.e. NSAIDs).

Highlight potential for confusion for patients whose olmesartan dose is increased from 20 mg to 40 mg. For both monotherapy and combination therapy, the 20 mg and 40 mg tablets are the same colour and only differ in shape (see Table 2), although the packaging colours differ.

Suggest or provide the Olmetec or Olmetec Plus consumer medicine information (CMI) leaflet (available at www.nps.org.au/consumers).

Table 2: Dose strengths, appearance and availability of olmesartan and olmesartan/hydrochlorothiazide^{4,18}

Doses	Packet: logo colour	Tablet: colour, shape	Availability in Australia
Olmesartan			
10 mg	N/A	N/A	✗
20 mg	Light green	White, circular	✓
40 mg	Light blue	White, oval	✓
Olmesartan/ hydrochlorothiazide			
20 mg/12.5 mg	Dark blue	Reddish-yellow, circular	✓
20 mg/25 mg	N/A	Pinkish, circular	✗
40 mg/12.5 mg	Orange	Reddish-yellow, oval	✓
40 mg/25 mg	Pink	Pinkish, oval	✓

N/A = not applicable

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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 clinical circumstances of each patient.