Olmesartan, amlodipine and hydrochlorothiazide are combined in a new triple fixed-dose combination (FDC)
The triple FDC formulation has been shown to lead to a greater reduction in BP compared with dual combinations of the individual components.

The triple FDC formulation is not appropriate for people with newly diagnosed hypertension
Only use this formula in people who have established hypertension and who are currently taking two or more of the individual components.

The triple FDC formulation is PBS listed as a restricted benefit
It is PBS subsidised in patients whose hypertension is not well controlled on dual combinations consisting of an angiotensin-II receptor antagonist, dihydropyridine calcium channel blocker or thiazide diuretic.

There are no trial data showing clinical benefit of the FDC over the individual components
It is not known whether the triple FDC confers any clinical benefit, either through greater efficacy or improved adherence, over concomitant use of olmesartan, amlodipine and hydrochlorothiazide taken separately.

What is it?
The olmesartan/amlodipine/hydrochlorothiazide triple FDC contains three antihypertensive medicines:
- an angiotensin-II receptor blocker: olmesartan medoxomil
- a dihydropyridine calcium channel blocker: amlodipine besilate
- a thiazide diuretic: hydrochlorothiazide.
Each of the active ingredients targets a different mechanism to reduce BP.
Olmesartan medoxomil is an angiotensin-II receptor antagonist with a high affinity for the angiotensin-II receptor type 1 (AT1) receptor. Olmesartan reduces BP by blocking angiotensin-II binding to the AT1 receptor, thereby reducing the associated vasoconstricting and aldosterone-secreting effects.
Amlodipine is a peripheral arterial dilator that acts selectively on vascular smooth muscle cells by inhibiting calcium ion influx across cell membranes. This causes a reduction in BP by reducing peripheral vascular resistance.¹

Hydrochlorothiazide is a thiazide diuretic that affects the renal tubular mechanisms of electrolyte reabsorption, increasing excretion of sodium and chloride in equal amounts.¹

Who is it for?
Olmesartan with amlodipine and hydrochlorothiazide may be an option in people with hypertension not well controlled on a combination of the individual components of the triple FDC. People with newly diagnosed hypertension should not be started on the triple FDC.

The National Heart Foundation guidelines state that FDC products may be a convenient option for people after a combination regimen is established.⁴ For people with hypertension who are not currently being treated with any of the components of the olmesartan/amlodipine/hydrochlorothiazide FDC an initial trial of the individual components to optimise dose and monitor for side effects is recommended.

Where does it fit?
The indications and targets for treating hypertension depend on the presence or absence of comorbidities (particularly cardiovascular disease, diabetes, and chronic kidney disease) and on an assessment of absolute cardiovascular disease risk.⁴,⁵ The first-line management of hypertension is based on lifestyle advice and behaviour modification as appropriate.⁴,⁶

Guidelines recommend starting patients with hypertension on a single agent then either increasing the dose of that agent or adding an additional agent to achieve target BP.⁴ Studies have shown that most patients will not reach BP targets with monotherapy.⁴,⁵ Most patients will require a combination of medicines from two or more classes.⁴

Olmesartan with amlodipine and hydrochlorothiazide FDC is an option for treating people for whom dual therapy with two of the components does not provide sufficient lowering of BP.

How does it compare?
Efficacy of the olmesartan with amlodipine and hydrochlorothiazide triple FDC has been compared with that of dual combinations of the individual components for reducing BP in the TRINITY trial, a multicentre, randomised, double-blind parallel-group study of 2492 patients with moderate to severe hypertension.⁷

The primary objective of the TRINITY trial was to determine whether combining olmesartan with amlodipine and hydrochlorothiazide would result in a clinical benefit in terms of reduced seated diastolic BP (SeDBP) compared with dual combinations of the individual products.⁷

The study population was mainly obese, with 62.4% of patients having a BMI ≥ 30 kg/m². Comorbidities in the patient population included diabetes (15.5%), chronic kidney disease (4.1%) and chronic cardiovascular disease (9.1%).

The trial was randomised, double-blind and of 12-weeks’ duration. After an initial 3-week washout period patients were randomised to three groups receiving an FDC comprising:

- olmesartan 40 mg plus amlodipine 10 mg
- olmesartan 40 mg plus hydrochlorothiazide 25 mg
- amlodipine 10 mg plus hydrochlorothiazide 25 mg.

Patients remained on dual therapy for 4 weeks, after which half the patients in each group were switched to triple combination therapy of olmesartan 40 mg with amlodipine 10 mg and hydrochlorothiazide 25 mg until week 12.⁶

**Triple combination therapy effectively lowers BP**
Not surprisingly, in the trial, treatment with triple combination therapy was associated with a significantly greater reduction in both SeDBP and SeSBP compared with dual treatments at 12 weeks (p < 0.001 for all treatment comparisons; Table 1).

Patients treated with the triple combination therapy were also more likely to reach BP targets than those treated with dual combination therapies.
Olmesartan with amlodipine and hydrochlorothiazide (Sevikar HCT)

WHAT IS KNOWN ABOUT THIS DRUG?
The olmesartan with amlodipine and hydrochlorothiazide triple FDC product combines three antihypertensive medicines.

The triple FDC was shown to be more effective in terms of BP lowering than combinations of any two of the three components; however, it is not known whether this translates into reductions in cardiovascular mortality or morbidity.

AREAS OF UNCERTAINTY
It is not known whether the triple FDC product is more effective than concomitant use of the separate components, either through greater efficacy or through improved adherence to treatment.

Although FDC medicines are associated with significant improvements in adherence, improved adherence may not translate to improved health outcomes.

WHAT DOES NPS SAY?
The triple FDC product may be an option for people whose hypertension is currently not well controlled on two of the individual components taken separately. It may also be an option for people currently taking the three individual components separately and who would like to rationalise their medicines into one tablet.

The PBS restriction does allow for patients who are currently taking combinations of medicines from the individual classes; however, patients should be stabilised on the individual components of a combination therapy before switching to the combined preparation.

Convenience and cost saving to the patient are also factors in the decision to switch to an FDC.

Four of the five available dose combinations contain the higher dose of olmesartan. With the combination containing the lower dose of olmesartan there are no options to up-titrate the amlodipine and diuretic components. This may be an issue for some prescribers.

Consider requesting a Home Medicines Review for people transitioning to FDC formulations from individual components.

EVIDENCE SNAPSHOT
Is the triple FDC product better than concomitant use of separate components?
There is currently no clinical evidence that use of the triple FDC product will result in any greater lowering of BP than concomitant use of the three components separately.

Some studies have indicated there may be an adherence advantage for combination products. However, there is currently no clinical evidence demonstrating improved adherence when using the triple FDC product over either the individual products taken separately, or individual products taken in conjunction with dual combination products.

Regardless of clinical benefit, an FDC tablet may reduce pill burden and out-of-pocket cost and be more convenient for the patient, with an associated improvement in adherence.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean reduction in seated diastolic BP at 12 weeks</th>
<th>Mean reduction in seated systolic BP at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple therapy</td>
<td>21.8 mmHg</td>
<td>37.1 mmHg</td>
</tr>
<tr>
<td>Olmesartan/amlodipine</td>
<td>18.0 mmHg</td>
<td>30.0 mmHg</td>
</tr>
<tr>
<td>Olmesartan/hydrochlorothiazide</td>
<td>16.9 mmHg</td>
<td>29.7 mmHg</td>
</tr>
<tr>
<td>Amlodipine/hydrochlorothiazide</td>
<td>15.1 mmHg</td>
<td>27.5 mmHg</td>
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</tbody>
</table>

Table 1.
Least squares mean change in blood pressure

NPS MedicineWise
Effect on reduction in cardiovascular risk
There are currently no trials demonstrating reduced cardiovascular risk in patients with hypertension treated with the olmesartan/amlodipine/hydrochlorothiazide FDC.¹

Comparison with other triple FDC products
There is currently one other triple FDC product for hypertension PBS listed in Australia — valsartan with amlodipine and hydrochlorothiazide (Exforge HCT). The valsartan FDC has been compared with dual combinations of the individual components and achieved similar results to those from the TRINITY trial.¹⁴

There has been only one head-to-head trial comparing the efficacy of the valsartan triple FDC with that of the olmesartan triple FDC.¹⁵ This was a small open-label study (180 participants) with only a short-term follow-up (4 weeks).

The findings showed that both the valsartan triple FDC and the olmesartan triple FDC lowered BP to a greater extent than dual combinations of the components. Treatment with the valsartan triple FDC was associated with a small, but statistically significant, greater reduction in diastolic BP compared with that seen with the olmesartan triple FDC (31.5/25.4 mmHg vs 31.2/24.4 mmHg, respectively).

However, the size of the study and the length of the follow-up means the clinical relevance of the results is uncertain.

Safety issues
There is no clinical evidence that the olmesartan with amlodipine and hydrochlorothiazide triple FDC is associated with more adverse events than dual combinations of the individual products.⁷

In the TRINITY trial 28.2% of patients treated with the triple FDC experienced treatment-related adverse events compared with 23.2% of patients treated with olmesartan/amlodipine combination, 20.9% of patients treated with olmesartan/hydrochlorothiazide combination and 29.7% of patients treated with amlodipine/hydrochlorothiazide combination.⁷

The most common adverse events included dizziness, headache and fatigue. Peripheral oedema was more common in patients treated with combinations containing amlodipine (7.0–8.3% compared with 1% in patients taking the olmesartan/hydrochlorothiazide combination).⁷

Safety in older people and those with comorbidities
Although efficacy and safety of the individual components of the FDC are well established, the safety of the olmesartan/amlodipine/hydrochlorothiazide FDC has not been established in a number of important populations in clinical trials, such as in older people.

The average age of patients in the TRINITY trial was 55.1; about 80% of the study population were under 65 and only around 3% were over 75.⁷ This may be a concern given that most people over 65 in Australia have hypertension.⁶

People with uncontrolled diabetes were also excluded from the trial, as were those with recent or current coronary artery disease.⁷

Intravascular volume depletion
As with all medicines containing thiazide diuretics, hypotension may occur in patients who are volume or sodium depleted, such as from diarrhoea and vomiting.¹

As with all medicines containing angiotensin-II receptor antagonists, people in whom vascular tone and renal function is particularly dependent on the normal activity of the renin–angiotensin–aldosterone system, such as those with severe congestive heart failure or chronic kidney disease, may be at risk of acute hypotension, oliguria and acute renal failure.

There is also increased risk of severe hypotension and renal insufficiency in people with bilateral renal artery stenosis, or stenosis of the artery to a single functioning kidney.¹

Cardiovascular considerations
As with other medicines containing amlodipine, the olmesartan/amlodipine/hydrochlorothiazide triple FDC should not be used in people who have had a recent myocardial infarct (within 4 weeks), who have unstable angina, aortic or mitral valve stenosis or obstructive hypertrophic cardiac myopathy.
Renal and hepatic impairment
Do not use the olmesartan/amlodipine/hydrochlorothiazide triple FDC in people with severe renal impairment (CrCl < 20 mL/min). The triple FDC is also contraindicated in patients with severe hepatic impairment (Child–Pugh score 10–15), cholestasis or biliary obstruction. 1
Routine monitoring of serum potassium and creatinine levels is recommended. 1

Caution with fixed-dose combination products
A recent meta-analysis found that use of combination antihypertensive products was associated with significantly improved adherence and persistence of therapy compared with patients taking the components separately. 9

There was no significant difference in efficacy between patients taking the FDC product of two antihypertensives and those taking the agents separately. 9 This is an interesting result, given that improved adherence might be expected to result in increased antihypertensive efficacy. Whether improved adherence translates into a reduction in cardiovascular mortality and morbidity is also unclear. 9,11–13

While improved adherence is a benefit of using FDC products, other issues with their use may impact on the benefit achieved. There is a risk that patient confusion about which medicines a combination product replaces may lead to inadvertent double dosing, and the potential adverse consequences of this are significant. Before starting the FDC, review the patient’s current medicines and advise the patient to stop taking any medicines that the FDC will replace and to return unused medicines to their pharmacy.

As with many FDC products, patient confusion may be compounded by brand names that are similar to products containing the individual components. In the case of the olmesartan/amlodipine/hydrochlorothiazide triple FDC the product brand name is Sevikar HCT, while the dual combination product is Sevikar. However, the packaging is distinctive to help differentiate these two. Consider requesting a Home Medicines Review for people transitioning to the triple FDC.

There is also an issue that emergent adverse effects cannot be definitively attributed to the particular causal agent when combination products are used. This risk may be reduced by stabilising patients on equal doses of individual components before switching to the combination product. However, a recent Australian study found that, in patients prescribed FDC antihypertensives, only a minority had been first stabilised on the individual components. 17

Establishing an effective combination and dose regimen using individual products is recommended before switching patients to FDC products. 4

This study only looked at dual FDC products, so this risk may be reduced when using a triple FDC product. However, a proportion of patients on a triple FDC may require additional doses of individual components, or even require a fourth component to be added, 4 which may negatively affect the adherence benefit of FDC products. 17

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed with the October issue of Australian Prescriber.

Reason for PBS listing
The PBAC recommended the listing of the olmesartan with amlodipine and hydrochlorothiazide triple FDC as a restricted benefit for treatment of hypertension on a cost-minimisation basis compared with the individual components given concomitantly.
Dosing issues

The olmesartan with amlodipine and hydrochlorothiazide triple FDC is available in five strengths (Table 2). The recommended dosage is one tablet taken daily with or without food. Starting dose will depend on pre-existing doses of individual components. Be aware that there is only one combination available with the lower dose of olmesartan, limiting options for up-titration of the amlodipine and diuretic components in patients requiring a lower dose of olmesartan.

Pregnancy, lactation and paediatric use

Do not use the olmesartan triple FDC in pregnant women, in women who are breastfeeding or in children or adolescents.

Electrolyte imbalance

Serum electrolyte levels should be determined at regular intervals, at least twice a year. The olmesartan/amlodipine/hydrochlorothiazide triple FDC is contraindicated in patients with refractory hypokalaemia, hypercalcaemia, hyponatraemia and uncontrolled gout.1

As with other medicines containing diuretics and angiotensin-II receptor antagonists, close monitoring of serum potassium levels is recommended for at-risk patients such as those with renal impairment, diabetes or heart failure.

Drug interactions

Use of NSAIDs is not recommended while taking an olmesartan triple FDC. Concomitant use of an angiotensin-II receptor antagonist, thiazide diuretic and NSAID increases the risk of renal impairment.18

If this combination is necessary, more frequent monitoring of serum creatinine is advised.1

Particular caution should be taken with this combination in elderly people, or people with renal insufficiency.1

As with all angiotensin-II receptor antagonists and thiazide diuretics, treatment should not be combined with lithium.1

Antidiabetic medicines

Although the dose of thiazide diuretic is low, there may be an effect on glucose tolerance, and antidiabetic medicine doses may need to be adjusted.

Drug metabolism effects

The action of the olmesartan/amlodipine/hydrochlorothiazide FDC is affected by consumption of grapefruit juice, and by the concomitant use of CYP3A4 inhibitors. For more information refer to the Product Information.

Information for patients

Patients may benefit from a full Home Medicines Review when they start the triple FDC formulation.

Explain to patients that the triple FDC replaces all antihypertensive medicines (unless taking additional doses or a fourth agent).

Ensure patients are aware that the brand names for the dual and triple combinations of olmesartan are similar — Sevikar and Sevikar HCT.

Ensure patients know there will be an ongoing need for monitoring when taking the triple FDC and that they may need to take additional doses of antihypertensive medicines in the future.

Advise patients to:

▸ return previous supplies of antihypertension medicines to their pharmacy to avoid inadvertent overdose
▸ avoid grapefruit juice
▸ seek medical advice before taking NSAIDs, even those available over the counter or from supermarkets.

Discuss the Sevikar HCT Consumer Medicine Information (CMI) leaflet* with the patient.

<table>
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<tr>
<th>Olmesartan</th>
<th>Amlodipine</th>
<th>Hydrochlorothiazide</th>
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<tr>
<td>20 mg</td>
<td>5 mg</td>
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NSAIDs: non-steroidal anti-inflammatory drugs CYP: cytochrome P
REFERENCES


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The information contained in NPS RADAR is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in NPS RADAR should be made in the context of the clinical circumstances of each patient.

NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

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