Lercanidipine and enalapril combination therapy for the treatment of hypertension

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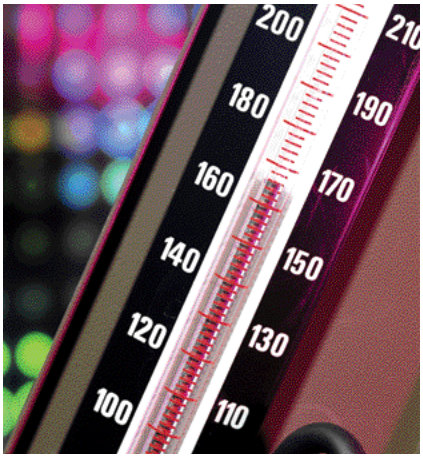

PHOTOLIBRARY

Lercanidipine plus enalapril (Zan-Extra) has been approved for use in patients with hypertension who have not reached blood pressure targets after treatment with either lercanidipine or enalapril monotherapy.

What is lercanidipine plus enalapril combination therapy?

Lercanidipine plus enalapril (Zan-Extra) is a fixed dose combination antihypertensive medication, which consists of the dihydropyridine calcium channel blocker lercanidipine (Zanidip) and the angiotensin converting enzyme (ACE) inhibitor enalapril. There are two doses available: lercanidipine 10 mg plus enalapril 10 mg (Zan-Extra 10/10) and lercanidipine 10 mg plus enalapril 20 mg (Zan-Extra 10/20).

In whom is it used?

Combination therapy with lercanidipine and enalapril has been approved by the TGA. It is available on the PBS (restricted benefit) for use in patients with hypertension who have not reached their target blood pressure levels after treatment with either lercanidipine or enalapril monotherapy. Thus any patient with hypertension who has been treated with monotherapy of lercanidipine 10 mg per day or enalapril 10 mg or 20 mg per day is eligible for treatment with combined lercanidipine plus enalapril.

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Further evidence now suggests that ACE/calcium channel blocker should be used in preference to ACE/thiazide as combination therapy. Thus lercanidipine plus enalapril combination therapy would be the preferred next titration step in patients taking enalapril.

How is it used?

Combined lercanidipine and enalapril can be initiated in patients who have not attained blood pressure targets with either lercanidipine or enalapril monotherapy. Three scenarios therefore precede the initiation of combined therapy, as described below.

- Patients with hypertension who are not at blood pressure target and are receiving lercanidipine 10 mg daily monotherapy. In these patients, combination therapy with lercanidipine 10 mg plus enalapril 10 mg can be introduced as the next titration step in therapy. If after eight weeks of this combined therapy the patient's blood pressure is still not at target, the dose should be increased to lercanidipine 10 mg plus enalapril 20 mg.
- Patients with hypertension who are not at blood pressure target and are receiving enalapril 10 mg daily monotherapy. The trials that have been performed with combined lercanidipine plus enalapril have assumed that enalapril would be titrated to 20 mg daily as monotherapy before initiation of combination therapy. However, Australian guidelines have recommended that in initiating therapy the initial agent be commenced at low dose and a second agent (also at low dose) added if patients have not achieved target blood pressure with the first agent alone. In keeping with these guidelines, lercanidipine 10 mg plus enalapril 10 mg combined therapy could be used as the next titration step after enalapril 10 mg daily as monotherapy. A further titration to lercanidipine 10 mg plus enalapril 20 mg could then occur if the patient has not achieved the target blood pressure after eight weeks.
- Patients with hypertension who are not at blood pressure target and are receiving enalapril 20 mg daily monotherapy. In these patients, lercanidipine 10 mg plus enalapril 20 mg combined therapy may be commenced as the next therapeutic step.

In addition, patients who have attained their blood pressure target and are receiving lercanidipine 10 mg and enalapril either 10 or 20 mg as individual agents should be transferred to the combined agent as reduced tablet numbers have been shown to aid compliance.

What needs monitoring?

ACE inhibitors such as enalapril may result in hyperkalaemia and decreasing

renal function. The latter may occur in patients with chronic renal disease in the absence of renal artery stenosis. Serum potassium and creatinine levels should therefore be monitored at appropriate intervals. Lercanidipine and enalapril may cause elevation in liver enzymes and bilirubin; therefore these levels should be monitored. Enalapril may worsen anaemia in patients with chronic renal disease; therefore, haemoglobin levels should be monitored.

In patients with bipolar disorder who are taking lithium, the serum lithium levels should be monitored as lithium clearance may be reduced by enalapril. However, in patients with bipolar disorder and hypertension, the use of other psychotrophics with ACE inhibitor therapy or the use of lithium with other antihypertensive agents is preferred.

Common side effects

The side effects of the combination therapy lercanidipine plus enalapril are essentially those of the individual agents, although some side effects may be due to both agents. The most common side effect of enalapril is cough. Other common side effects include rash, dyspnoea, diarrhoea, taste disturbance (metallic taste), headache and blurred vision. Although rare, the most important side effect of enalapril is angio-oedema.

Lercanidipine generally has a low side-effect profile with a lesser occurrence of oedema, headache and flushing than other calcium channel blockers. Diarrhoea has been reported, rather than constipation.

With lercanidipine plus enalapril combined therapy, the side effects that may be attributable to either one of the agents or to both agents in combination are cough, headache, flushing, diarrhoea and rash.

Important precautions and interactions

ACE inhibitors can cause acute renal failure in a fetus, resulting in oligohydramnios and death *in utero*. Calcium channel blockers other than lercanidipine have been shown to be teratogenic. Lercanidipine plus enalapril should, therefore, not be prescribed to women during pregnancy, to women seeking to become pregnant or to those who are breastfeeding (because both agents are excreted in breast milk).

Both lercanidipine and enalapril are vasodilators, therefore, the combination therapy should be given with caution in patients who have left ventricular valvular or outflow obstruction (aortic or mitral valve stenosis, hypertrophic cardiomyopathy) and avoided in patients with haemodynamically significant obstruction.

The main drug interactions of lercanidipine plus enalapril are those with agents that inhibit, induce or are metabolised by cytochrome P450 (CYP) isoenzymes. Thus drugs such as ketoconazole, itraconazole, erythromycin, ritonavir and fluoxetine that inhibit CYP3A4 may increase the plasma concentration of lercanidipine. Alternatively, agents such as rifampicin, phenytoin and carbamazepine, which induce CYP3A4, will accelerate lercanidipine metabolism and may reduce its antihypertensive effect. Coadministration of lercanidipine with other substrates of CYP3A4 (e.g. cyclosporin), and class III antiarrhythmic drugs (e.g. amiodarone and quinidine) may result in elevated levels of these agents and toxic effects may occur.

As with ACE inhibitor monotherapy, caution and frequent monitoring should be used if lercanidipine plus enalapril and potassium-sparing agents such as spironolactone, eplerenone, triamterene or amiloride are coadministered because of the propensity for increased potassium retention. Coadministration of NSAIDs including COX-2 inhibitors may reduce the antihypertensive efficacy of lercanidipine plus enalapril combination therapy and in some patients decrease renal function.

Summary

In summary, combination therapy with lercanidipine and enalapril provides a useful addition to our therapeutic armamentarium for the treatment of hypertension. Furthermore, this combination therapy reduces total tablet numbers and, therefore cost, which may help improve compliance. MT

COMPETING INTERESTS: None.