

Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

Therapeutic Class:

Angiotensin Converting Enzyme Inhibitors in combination with Calcium Channel Blockers

Overview:

Angiotensin Converting Enzyme (ACE) inhibitors are a class of medications used to manage hypertension. ACE inhibitors compete with angiotensin I for its binding site on the angiotensin-converting enzyme. As a result, ACE inhibitors block the conversion of angiotensin I to angiotensin II; angiotensin II is a potent vasoconstrictor. When angiotensin II is blocked, there is an increase in plasma renin activity. Decreases in plasma angiotensin II levels also result in a reduction of aldosterone secretion, with a subsequent decrease in sodium and water retention. ACE inhibitors are very effective in reducing blood pressure. Since they reduce glomerular blood pressure, these agents also have shown some renoprotective effects.

Calcium channel blockers (CCBs) exert their pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells. Serum calcium levels are not affected by CCBs. There are two classifications of CCBs: dihydropyridine and non-dihydropyridine. Felodipine and amlodipine are dihydropyridine calcium channel blockers. These agents inhibit the influx of extracellular calcium into cells of smooth muscles lining arteriolar walls resulting in increased oxygen delivery to the myocardial tissue, smooth muscle relaxation, vasodilation, decreased total peripheral resistance, decreased systemic blood pressure and decreased afterload. Verapamil, a phenylalkylamine calcium channel blocker, inhibits influx of extracellular calcium into cardiac and vascular smooth muscle cells resulting in inhibition of contractile processes of these muscles. The result is dilation of the main coronary artery (antianginal effect), systemic arteries (antihypertensive effect), and decreased heart, AV nodal conduction and myocardial contractility. Verapamil has a more pronounced effect on cardiac tissue than dihydropyridine CCBs.

The fixed-dose combinations of CCBs and ACE inhibitors are approved by the FDA for the treatment of hypertension. However, they are not indicated as an initial therapy. There is data supporting use of these fixed-dose combinations in treatment-resistant patients. Currently there are three fixed-dose CCB/ACE combination products available in the U.S. market. Only Lotrel[®] is available generically.

Generic Name	Trade Name	Dose	Manufacturer
Benazepril/Amlodipine	Lotrel [®]	2.5/10, 5/10, 5/20, 10/20,5/40, and 10/40 mg	Novartis
Trandolapril/Verapamil ER	Tarka [®]	1/240, 2/180, 2/240, and 4/240 mg	Abbott
Enalapril/Felodipine	Lexxel [®]	5/2.5 and 5/5 mg	AstraZeneca

Summary:

Given the benefit for treatment-resistant patients, at least one combination product should be added to the preferred drug list. Studies support the efficacy and safety of these agents in most populations. These agents have synergistic antihypertensive effects. PDL inclusion should be based on clinical trials comparing the safety and efficacy of these combination products.