



Focus on....

Co-Copalia® tablets

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Introduction

Hypertension treatment guidelines are aligned to reduce the burden of disease. However, achieving target blood pressure remains a challenge. Most patients require more than one antihypertensive agent to achieve target blood pressure, with many patients needing three or more agents.^{1,2}

Co-Copalia® combines three antihypertensive agents that complement each other to control blood pressure.³

Co-Copalia® tablets

Co-Copalia® film-coated tablets contain amlodipine (dihydropyridine calcium-channel blocker [DHP-CCB]), valsartan (angiotensin II receptor blocker [ARB]), and a thiazide diuretic, hydrochlorothiazide (HCTZ).³

Co-Copalia® is available in five different strengths:³

- Co-Copalia® 5 mg/160 mg/12.5 mg: Each film-coated tablet contains 6.94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 12.5 mg hydrochlorothiazide.
- Co-Copalia® 10 mg/160 mg/12.5 mg: Each film-coated tablet contains 13.87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 12.5 mg hydrochlorothiazide.
- Co-Copalia® 5 mg/160 mg/25 mg: Each film-coated tablet contains 6.94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide.
- Co-Copalia® 10 mg/160 mg/25 mg: Each film-coated tablet contains 13.87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide.
- Co-Copalia® 10 mg/320 mg/25 mg: Each film-coated tablet contains 13.87 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 320 mg of valsartan and 25 mg hydrochlorothiazide.

Indications

Co-Copalia® is indicated for the treatment of hypertension in patients stabilised on the individual components given at the same doses and not for the initial therapy of hypertension.³

Dosing and administration

The recommended dose is one tablet per day, taken with or without food.³

Important dosing considerations:³

- Patients stabilised on treatment with the individual components of Co-Copalia® may be switched to Co-Copalia® containing the same individual doses.
- The maximum dose of Co-Copalia® is 10 mg/320 mg/25 mg.
- The tablet should not be taken if there are any signs of cracking.

Mechanism of action

Amlodipine exerts its hypertensive effect by inhibiting the entry of calcium ions into cardiac and vascular smooth muscle. In doing so, amlodipine relaxes vascular smooth muscle, thereby reducing peripheral vascular resistance, widening blood vessels and reducing blood pressure.³

Valsartan acts on the angiotensin I receptor subtypes to block angiotensin II's effects, thereby widening blood vessels to allow blood to flow more easily, which lowers blood pressure.³

Hydrochlorothiazide works in the kidneys to increase the excretion of sodium and chloride ions, thereby reducing plasma volume and consequently increasing plasma renin activity, aldosterone secretion and urinary potassium loss.³

Pharmacokinetics

After oral administration of Co-Copalia®, the peak plasma concentrations of amlodipine, valsartan and HCTZ are reached in 6 to 12 hours, 2 to 4 hours, and 2 hours, respectively.³

Amlodipine is extensively metabolised in the liver with 10% of the parent compound and 60% of the metabolites excreted in the

urine. The terminal elimination half-life is approximately 30 to 50 hours, with steady-state plasma levels reached after 7 to 8 days of continuous administration.³

Transformation of valsartan is extensive as only about 20% of the dose is recovered as metabolites. It is mostly eliminated in faeces and to a lesser extent in urine, mainly as an unchanged compound. The half-life of valsartan is six hours.³

HCTZ is eliminated unchanged in the urine, accounting for more than 95% of the absorbed dose. Accumulation is minimal when dosed once daily as there is no change in the kinetics of HCTZ.³

Efficacy

In combination, amlodipine/valsartan/HCTZ have an additive antihypertensive effect, reducing blood pressure to a greater extent than the components alone.³

The efficacy of the individual components of Co-Copalia® has an established role in treating hypertension.¹ The safety and efficacy of dual combinations, valsartan/HCTZ and amlodipine/valsartan are also well established in hypertension.² Most studies testing the triple combination of amlodipine/valsartan/HCTZ compare it to dual therapies, with results favouring this triple therapy combination for significant reductions in blood pressure.⁴

Besides producing a more significant decrease in blood pressure, a large phase III randomised trial by Deeks reported the proportion of patients achieving overall blood pressure control was significantly greater with the triple combination regimen than with any of the dual regimens independent of age, race, gender and ethnicity.⁵

Compared to dual therapies, triple therapy with valsartan, amlodipine and HCTZ produced robust reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP).²

Treatment group	Mean change in SBP (mmHg)	Mean change in DBP (mmHg)
Aml/Val/HCTZ 10/320/25 mg	-39.7	-24.7
Val/HCTZ 320/25 mg	-32	-19.7
Aml/Val 10/320 mg	-33.5	-21.5
Aml/HCTZ 10/25 mg	-31.5	-19.5

SBP – systolic blood pressure, DBP – diastolic blood pressure, Aml – amlodipine, Val – valsartan, HCTZ –hydrochlorothiazide

The phase III CVEA489A2302 study, which played a key role in the European approval of the amlodipine, valsartan and HCTZ combination, demonstrated a reduction in SBP of 40 to 50 mmHg.⁶ Up to 58% more patients on the triple combination achieved overall BP control compared to dual combination therapy. Additionally, ambulatory blood pressure monitoring showed that the blood pressure-lowering effect of triple therapy was maintained throughout a 24 - hour period.⁴

Safety

Contraindications³

- Hypersensitivity to any of the active ingredients and excipients of Co-Copalia®
- Pregnancy and lactation. Treatment with Co-Copalia® should be discontinued as soon as possible when pregnancy is suspected
- A history of angioedema related to previous therapy with ARBs
- Hereditary or idiopathic angioedema
- Severe hepatic impairment
- Patients with Addison's disease
- Anuria, severe renal impairment (creatinine clearance less than 30 ml/min)
- Lithium therapy
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia
- Porphyria
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium-sparing diuretics
- Use in patients under 18 years

Precautions and drug interactions

Valsartan and the concomitant use of medicines that may increase potassium levels require monitoring of potassium levels.³

The following excerpt is taken from the package insert for Co-Copalia®. The most clinically significant drug interactions were found with the thiazide component of Co-Copalia®.³

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may weaken the diuretic and antihypertensive effect of HCTZ.
- Medicinal products affecting potassium: The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives.
- Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digoxin-induced cardiac dysrhythmias.
- Antidiabetic medicinal products: the dosage of insulin and of oral antidiabetic agents may require readjusting.
- Anticholinergic agents: The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents.
- Methyl dopa: There have been reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyl dopa.
- Cholestyramine: reduces the absorption of thiazide diuretics.
- Vitamin D and calcium salts: thiazide diuretics may potentially increase serum calcium.

- Cyclosporin: The risk of hyperuricaemia and gout-related complications may be increased.
- Carbamazepine: hyponatraemia may develop; therefore, monitoring is necessary.
- Cytotoxic agents (cyclophosphamide, methotrexate): myelosuppressive effects may be increased due to reduced renal excretion.

Please refer to the package insert of Co-Copalia® for a full list of drug interactions.

Side effects

Most side effects reported in a clinical study were mild to moderate in severity. The most common side effects reported were peripheral oedema, headache and dizziness. Dyspepsia, fatigue, muscle spasms, back pain, nasopharyngitis and nausea were reported in more than 10% of patients treated with amlodipine/valsartan/HCTZ combination.² For a full list of side effects, refer to the package insert of Co-Copalia®.

Conclusion

Although hypertension is a treatable condition, achieving blood pressure control remains a challenge. The majority of patients with

moderate to severe hypertension often need multiple medications for blood pressure control. A triple combination regimen offers superior blood pressure control compared to dual regimens in these patients.⁴ The combination of amlodipine, valsartan and HCTZ in Co-Copalia® has an additive antihypertensive effect, reducing blood pressure to a greater extent than each component alone. Furthermore, this triple combination option provides a convenient, simplified, once-daily dosing in a single tablet for patients stabilised on these individual components.^{3,4}

References

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