AMLOARB®
(IRBESARTAN AND AMLODIPINE BESYLATE TABLET)

Quantitative composition.
Amloarb -5: Each film coated tablet contains: Irbesartan BP 300mg and Amlodipine (as Besylate) BP 5.0mg
Amloarb -10: Each film coated tablet contains: Irbesartan BP 300mg and Amlodipine (as Besylate) BP 10.0mg
***Pharmaceutical form*:** Film coated tablet.
***Pharmacology*:** Irbesartan is Angiotensin II, the principal pressor agent of the renin-angiotensin system, is responsible for effects such as vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT_1 receptor than for the AT_2 receptor and no agonist activity. Irbesartan's inhibition of angiotensin II binding to the AT1 receptor leads to multiple effects including vasodilation, a reduction in the secretion of vasopressin, and reduction in the production and secretion of aldosterone. The resulting effect is a decrease in blood pressure. The mechanisms of the antihypertensive action of Amlodipine tablets are due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which Amlodipine tablets relieves angina has not been fully determined but Amlodipine tablets reduces total ischaemic burden by the following two actions. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements. The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm.
Pharmacokinetics: After oral administration, Irbesartan is well absorbed: studies of absolute bioavailability gave values of approximately 60-80%. Concomitant food intake does not significantly influence the bioavailability of Irbesartan. Plasma protein binding is approximately 96%, with negligible binding to cellular blood components. The volume of distribution is 53 - 93 litres. Following oral or intravenous administration of ^{14}C Irbesartan, 80-85% of the circulating plasma radioactivity is attributable to unchanged Irbesartan. Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is Irbesartan glucuronide (approximately 6%). Irbesartan exhibits linear and dose proportional pharmacokinetics over the dose range of 10 to 600 mg. Peak plasma concentrations are attained at 1.5 - 2 hours after oral administration. The total body and renal clearance are 157 - 176 and 3 - 3.5 ml/min, respectively. The terminal elimination half-life of Irbesartan is 11 - 15 hours. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. No dosage adjustment is necessary in female patients. Irbesartan AUC and C_{max} values were also somewhat greater in older subjects (≥ 65 years) than those of young subjects (18 - 40 years). However the terminal half-life was not significantly altered. No dosage adjustment is necessary in older people. Irbesartan and its metabolites are eliminated by both biliary and renal pathways. After either oral or IV administration of ^{14}C Irbesartan, about 20% of the radioactivity is recovered in the urine, and the remainder in the faeces. Less than 2% of the dose is excreted in the urine as unchanged Irbesartan. After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Indications: Treatment of essential hypertension. Amloarb tablet is indicated in patients whose blood pressure is not adequately controlled on Irbesartan or Amlodipine monotherapy.
***Administration and Dosage*:** To be taken orally, with or without food. The usual initial and maintaince dose of Amloarb is one tablet per day. Amloarb should be administered in patients whose blood pressure is not adequately controlled on monotherapy with Irbesartan or Amlodipine or for continuation of therapy for patients receiving Irbesartan and Amlodipine as separate tablets. Dose should be determined on case- by -case basis, based on patient response to therapy with the individual component and the desired antihypertensive response. The maximum recommended dose with Amloarb-10(300mg Irbesartan /10mg Amlodipine). Treatment should be adjusted based on blood pressure response. Elderly patients and patients with impaired renal function: In general no dosage reduction is necessary in elderly patient or patients with impaired renal function (regardless of the degree of impairment). Patients with impaired hepatic function: As the medicinal product contains Amlodipine, Amloarb should be administered with caution in these patients.
***Contraindications*:** Amloarb is contra-indicated in severe hypotension, shock (including cardiogenic shock), second and third trimesters of pregnancy, hypersensitivity to active substance, dihydropyridine derivatives or any of the excipients, in haemodynamically unstable heart failure after acute myocardial infarction (during the first 28 days) and obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).The concomitant use of Irbesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2).
***Warning and Precautions*:** Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group, but this was not indicating an aggravation of the heart failure. Calcium channel blockers, including Amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality. The half-life of amlodipine in is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, and diarrhoea or vomiting. Such conditions should be corrected before the administration of Irbesartan. There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system. When Irbesartan is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. As with other medicinal products that affect the renin-angiotensin-aldosterone system, hyperkalaemia may occur during the treatment with Irbesartan, especially in the presence of renal impairment, overt proteinuria due to diabetic renal disease, and/or heart failure. Close monitoring of serum potassium in patients at risk is recommended. As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
***Drug interaction*:** Concomitant use of Amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary, therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum). Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects. The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents. In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporine. The pharmacokinetic of Irbesartan is not affected by hydrochlorothiazide. Irbesartan is mainly metabolized by CYP2C9 and to a lesser extent by glucuronidation. No significant pharmacokinetic or pharmacodynamic interactions were observed when Irbesartan was coadministered with warfarin, a medicinal product metabolized by CYP2C9. The effects of CYP2C9 inducers such as rifampicin on the pharmacokinetic of Irbesartan have not been evaluated. The pharmacokinetic of digoxin was not altered by coadministration of Irbesartan.
***Pregnancy and Lactation*:** Amloarb is not recommended it carries greater risk for the mother and foetus. The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. Amlodipine is excreted in human milk and proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. Irbesartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant. It is unknown whether Irbesartan or its metabolites are excreted in human milk. Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Irbesartan had no effect upon fertility of treated rats and their offspring up to the dose levels inducing the first signs of parental toxicity
***Effects on ability to drive and use machines*:** If patients taking Amlodipine/irbesartan suffer from dizziness, headache, fatigue or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment. Based on its pharmacodynamic properties, Irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment.
Adverse reactions: Common side effects includes: Somnolence, dizziness, headache, Visual disturbance, Palpitations, Flushing, orthostatic hypotension, Dyspnoea, Oedema, Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation) and vomiting, Ankle swelling, muscle cramps, Fatigue and asthenia.
Other uncommon signs includes: Insomnia, mood changes (including anxiety), depression, Tremor, dyspepsia, syncope, hypoesthesia, paresthesis, Tinnitus, Arrhythmia, Hypotension, flushing, Rhinitis, cough, Vomiting, dry mouth. Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria, Impotence, gynecomastia, Micturition disorder, nocturia, increased urinary frequency, Arthralgia, myalgia, back pain Chest pain, pain and malaise.
***Overdosage and treatment*:** The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur. The patient should be closely monitored, and the treatment should be symptomatic and supportive for irbesartan. Amlodipine large overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome. Amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.
***Presentation*:** Blister packs of 3 x 10`s in a unit box.
Shelf life: 3 years from the date of manufacture.
Storage: Do not store above 30^0C. Protect from direct sunlight.**.** Keep all medicines out of reach of children.
***Distribution category*:** Prescription only medicine (POM).
Manufactured by:

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Ref: Lf /DL/ AMLOARB /00

Date of issue: October 2018