Olmesartan medoxomil
Amlodipine besilate

Olmezar-A

20 mg/5 mg Film-coated Tablet

ANTIHYPERTENSIVE

FORMULATION
Each film-coated tablet contains :
Olmesartan medoxomil 20mg
Amlodipine (as besilate)..... 5 mg

INDICATION
Treatment of essential hypertension. It is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy. This combination may also be used as initial therapy in patients who are likely to need multiple antihypertensive agents to achieve their blood pressure goals.

DOSAGE AND ADMINISTRATION
Adults: The recommended dosage is 1 tablet per day. It may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil or 5 mg amlodipine alone.

Dose Titration Guided by Clinical Effect
A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine calcium-channel blocker) alone or with olmesartan (or another angiotensin-II receptor blocker) alone may be switched to combination therapy with this fixed dose combination.

Replacement Therapy
For convenience, patients receiving amlodipine and olmesartan from separate tablets may instead wish to receive tablets of amlodipine + olmesartan containing the same components.

The safety and efficacy of this drug in children and adoloescents below 18 years has not been established. No data are available.

This can be taken with or without food. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed and should be taken at the same time of the day.

CONTRAINDICATIONS
Patients who are hypersensitive to any component of this product. Second and third trimesters of pregnancy. Lactation. Severe hepatic insufficiency. Biliary obstruction.
Due to the component amlodipine, it is also contraindicated in patients with severe hypotension, shock (including cardiogenic shock, obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis) and haemodynamically unstable heart failure after acute myocardial infarction.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Patients with hypovolaemia or sodium depletion:
Symptomatic hypotension may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting, especially after the first dose. Correction of this condition prior to administration of this drug or close medical supervision at the start of the treatment is recommended.

Other conditions with stimulation of the renin-angiotensin-aldosterone system:
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system, such as angiotensin II receptor antagonists, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

Renovascular hypertension:
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.

Renal impairment and kidney transplantation:
When this drug is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of this drug is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min) (see sections 4.2, 5.2). There is no experience of the administration of this drug in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance < 12 mL/min).

Hepatic impairment
Exposure to amlodipine and olmesartan medoxomil is increased in patients with hepatic impairment. Care should be taken when this drug is administered in patients with mild to moderate hepatic impairment . In moderately impaired patients, the dose of olmesartan medoxomil should not exceed 20 mg. In patients with impaired hepatic function, amlodipine should be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Use of this drug in patients with severe hepatic impairment is contraindicated.

Hyperkalemia
As with other angiotensin II antagonists and ACE inhibitors, hyperkalemia may occur during treatment with olmesartan medoxomil, especially in the presence of renal impairment and/or heart failure. Close monitoring of serum potassium levels in at risk patients is recommended.

Concomitant use with potassium supplement, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Lithium
As with other angiotensin-II receptor antagonists, the combination of lithium and Olmesartan medoxomil is not recommended.

A*ortic or mitral valve stenosis. Obstructive hypertrophic cardiomyopathy*
Due to the amlodipine content of this drug, as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmesartan medoxomil is not recommended in such patients.

Heart failure:
As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.
Patients with heart failure should be treated with caution. 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.

Ethnic differences:
As with all other angiotensin II antagonists, the blood pressure lowering effect of this drug can be somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.

Older people
In older people, increase of the dosage should take place with care.

Pregnancy:
Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Other
As with any antihypertensive agent, excessive blood pressure reductions in patients with ischemic heart disease or ischemic cerebrovascular disease could result in myocardial infarction or stroke.

PHARMACOLOGY
Mechanism of Action
Olmesartan
Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the AT_1 receptor. Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT_1) antagonist. It blocks all actions of angiotensin II mediated by the AT_1 receptor.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nonhydropyridine binding sites. The contractile processes of cardiac muscle and vsacular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.
Amlodipine is a peripheral arterial vasodilator that acts dirstly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

PHARMACOKINETICS
Olmesartan
Absorption and Distribution
Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. The mean absolute bioavailability of Olmesartan from a tablet form is 25.6%.
The mean peak plasma concentration (C_{max}) of Olmesartan is reached within about 2 hours after oral dosing with Olmesartan medoxomil. Olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80mg. Steady-state levels of Olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing. Food has minimal effect on the bioavailability of Olmesartan and therefore Olmesartan medoxomil may be administered with or without food. No clinically relevant gender-related differences in the pharmacokinetics of Olmesartan have been observed.
Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between Olmesartan and other highly bound co-administered drugs is low. The binding of Olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 L).
In rats, Olmesartan passes across the placental barrier and is distributed to milk.

Biotransformation and Elimination
Total plasma clearance is typically 1.3 L/h and was relatively slow compared to hepatic blood flow (90 L/h). Following a single oral dose of ^{14}C-labelled Olmesartan medoxomil, 10-16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (40%) and hepato-biliary excretion (60%). All recovered radioactivity as identified as Olmesartan. No other significant metabolite was detected. Enteroheopatic recycling of Olmesartan is minimal. Since a large portion of Olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated.
The terminal elimination half life of olmesartan varies between 12 and 15 hours after multiple dosing. Steady state is reached after the first few doses and no further accumulation is evident after 14 days or repeated dosing. Renal clearance is approximately 0.5 – 0.7 L/h and is independent of dose.

Amlodipine
Absorption and Distribution
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. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The absorption of amlodipine is unaffected by the concomitant intake of food.

Biotransformation and Elimination:
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.

Pharmacokinetics in special populations
Elderly
In hypertensive patients, the AUC at steady state was increased by 35% in elderly patients (65-75 years of age) and by 44% in elderly subjects 75 years of age or older compared with younger aged patients.

Renal Impairment
In renally impaired patients, the AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate, and severe renal impairment, respectively, compared to healthy controls.

Hepatic Impairment
After single oral administration, oral AUC values were 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26%, 0.34% and 0.41%, respectively. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment.

DRUG INTERACTIONS
To be taken into account with concomitant use
Other antihypertensive agents:
The blood pressure lowering effect of this drug can be increased by concomitant use of other antihypertensive medicinal products (e.g. alpha blockers, diuretics).

Potential interactions related to the **olmesartan medoxomil** component of this drug:
Concomitant use not recommended
Medicinal products affecting potassium levels:
Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin, ACE inhibitors) may lead to increases in serum potassium. If medicinal products which affect potassium levels are to be prescribed in combination with this drug, monitoring of serum potassium levels is recommended.
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II antagonists. Therefore concomitant use of this drug and lithium is not recommended. If concomitant use of this drug and lithium proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution
Non-steroidal anti-inflammatory medicinal products (NSAIDs) including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs:
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may increase the risk of worsening of renal function and may lead to an increase in serum potassium. Therefore monitoring of renal function at the beginning of such concomitant therapy is recommended, as well as adequate hydration of the patient.

Additional information
After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed.
Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin. Coadministration of olmesartan medoxomil with pravastatin had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.
Olmesartan had no clinically relevant inhibitory effects on human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4 *in vitro*, and had no or minimal inducing effects on rat cytochrome P450 activities. No clinically relevant interactions between olmesartan and medicinal products metabolised by the above cytochrome P450 enzymes are expected.

Potential interactions related to the **amlodipine** component of this drug:
Effects of other medicinal products on amlodipine
CYP3A4 inhibitors:
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 older people. Clinical monitoring and dose adjustment may thus be required.
CYP3A4 inducers:
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.
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.
Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products
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 cyclosporin.
Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

ADVERSE REACTIONS
The most commonly reported adverse reactions during treatment with this drug are peripheral oedema (11.3%), headache (5.3%) and dizziness (4.5%).
The following terminologies have been used in order to classify the occurrence of adverse reactions:
Very common (≥1/10)
Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Olmesartan + amlodipine combination
Common (≥1/100 to <1/10) : Dizziness; headache; fatigue; edema; peripheral edema; pitting edema;
Uncommon (≥1/1,000 to <1/100) : Hyperkalemia; decreased libido; hypoaesthesia; lethargy; paraesthesia; postural dizziness; vertigo; palpitations, tachycardia; hypotension; orthostatic hypotension; cough; dyspnea; constipation; diarrhea; dry mouth; dyspepsia; nausea; upper abdominal pain; vomiting; rash; back pain; muscle spasm; pain in extremity, pollakiuria; erectile dysfunction/impotence, asthenia; blood creatinine increased; blood potassium decreased; blood uric acid increased; gamma glutamyl transferase increased
Rare (≥1/10,000 to <1/1,000) : allergic reaction/hypersensitivity; syncope; flushing; urticaria; face edema;

Olmesartan
Common (≥1/100 to <1/10) : Hypertriglyceridemia; hyperuricemia; dizziness; headache; bronchitis; cough; pharyngitis; rhinitis; abdominal pain; diarrhea; dyspepsia; gastroenteritis; nausea; increased hepatic enzymes; arthritis; back pain; skeletal pain; hematuria; urinary tract infection; chest pain; fatigue; influenza-like symptoms; pain; peripheral edema; increased blood creatinine phosphokinase; increased blood urea
Uncommon (≥1/1,000 to <1/100) : Thrombocytopenia; anaphylactic reaction; vertigo; angina pectoris; vomiting; allergic dermatitis; exanthema; pruritus; rash; urticaria; myalgia; asthenia ; face edema; malaise;
Rare (≥1/10,000 to <1/1,000) : Hyperkalemia; hypotension; angioneurotic edema; muscle spasm; acute renal failure; renal insufficiency; lethargy; increased blood creatinine

Amlodipine
Very common (≥1/10)
Common (≥1/100 to <1/10) : dizziness; somnolence; flushing; abdominal pain; nausea; headache (especially at the beginning of the treatment); ankle swelling; fatigue; edema
Uncommon (≥1/1,000 to <1/100) : depression; insomnia; irritability; mood changes (including anxiety); dysgeusia; hypoaesthesia; paraesthesia; sleep disorder; syncope; tremor; visual disturbance (including diplopia); tinnitus; angina pectoris (including aggravation of angina pectoris); palpitations; hypotension; dyspnea; rhinitis; altered bowel habits (including diarrhea and constipation); dry mouth; dyspepsia; vomiting; alopecia; exanthema; hyperhydrosis; pruritus; purpura; rash; skin discoloration; arthralgia; back pain; muscle spasm; myalgia; increased urinary frequency; micturition disorder; nocturia; erectile dysfunction/impotence; gynecomastia; asthenia; chest pain; malaise; pain; weight decrease; weight increase;
Rare (≥1/10,000 to <1/1,000) : confusion;
Very rare (<1/10,000 : leukocytopenia; thrombocytopenia; allergic reaction/hypersensitivity; hyperglycemia; hypertonia; peripheral neuropathy; arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation); myocardial infarction; vasculitis; cough; gastritis; gingival hyperplasia; pancreatitis; increased hepatic enzymes (mostly consistent with cholestasis); hepatitis; jaundice; angioneurotic edema; erythema multiforme; exfoliative dermatitis; photosensitivity; Quincke edema; Stevens-Johnson syndrome; urticaria;

OVERDOSAGE
Symptoms:
There is no experience of overdose with the drug. The most likely effects of olmesartan medoxomil overdosage are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred. Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has been reported.
Treatment:
If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine.
Clinically significant hypotension due to an overdose of the drug requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. The dialysability of olmesartan is unknown.

STORE AT TEMPERATURES NOT EXCEEDING 30ºC.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Alu-Alu blister pack of 10's; box of 30's

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