Agen™
Amlodipine Besylate

ZENTIVA
A SANOFI COMPANY

FORMS AND PRESENTATION
Agen™ 5: Tablets: Box of 30.
Agen™ 10: Tablets: Box of 30.

COMPOSITION
Agen™ 5: Each tablet contains Amlodipine Besylate equivalent to Amlodipine 5mg.
Agen™ 10: Each tablet contains Amlodipine Besylate equivalent to Amlodipine 10mg.
Excipients: microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Calcium channel blockers.
ATC code: C08CA01.
Amlodipine is a calcium antagonist that inhibits the influx of calcium ions into the cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is the result of the direct relaxing effect on the arterial smooth muscle.
The mechanism that enables Amlodipine to reduce angina pectoris has not been completely clarified; however, the two following mechanisms are involved:
- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This reduction of the heart load leads to a reduction of the energy consumption as well as of the oxygen requirements of the myocardium.
- The dilatation of the main coronary vessels and coronary arterioles probably is involved in the mechanism of action of Amlodipine. This dilatation increases the myocardial oxygen supply in patients suffering from Prinzmetal's angina pectoris.

In patients suffering from hypertension, once daily administration produces a clinically significant reduction in blood pressure (both in lying and standing position), lasting for 24 hours.
In patients suffering from angina pectoris, once daily administration increases total exercise time, the time to occurrence of angina and the time to a 1 mm ST segment depression. Amlodipine reduces both the frequency of anginal attacks and the use of glyceryl trinitrate tablets.

Pharmacokinetic properties
Absorption
After oral administration of therapeutic doses, Amlodipine is slowly absorbed from the gastrointestinal tract. The bioavailability of Amlodipine is not influenced by concomitant intake of food. The absolute bioavailability of the unchanged active substance is approximately 64-80%. Peak plasma concentrations are reached within 6-12 hours after administration.
Distribution
The volume of distribution is approximately 20 l/kg. The pKa of Amlodipine is 8.6. In vitro plasma protein binding is approximately 98%.
Biotransformation
The plasma half-life varies between 35 and 50 hours. Steady-state plasma concentration is reached after 7-8 days.
Amlodipine is extensively metabolized into inactive metabolites.
Elimination
Approximately 60% of the administered dose is excreted in the urine, 10% of which is in a non-metabolized form.

INDICATIONS
Agen™ is indicated in:
- Essential hypertension.
- Chronic stable and vasospastic angina pectoris.

CONTRAINDICATIONS
Amlodipine is contraindicated in patients with:
- Hypersensitivity to dihydropyridine derivatives, Amlodipine or any of the excipients.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Hemodynamically unstable heart failure after acute myocardial infarction.

PRECAUTIONS
The safety and efficacy of Amlodipine in hypertensive crisis has not been established.
Patients with cardiac failure
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 edema was higher in the Amlodipine treated group than in the placebo group, but this was not associated with worsening of the heart failure.
Use in patients with impaired hepatic function
The half-life of Amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.
Use in elderly patients
In the elderly increase of the dosage should take place with care.
Use in renal failure
Amlodipine may be used in such patients at normal doses. Changes in Amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.
Ability to drive and use machines
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking Amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

PREGNANCY AND LACTATION
The safety of Amlodipine in human pregnancy has not been established.
Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labor at dosages 50 times greater than the maximum recommended dosage for humans.
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.
It is not known whether Amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of Amlodipine therapy to the mother.

DRUG INTERACTIONS
Effects of other medicinal products on Amlodipine
- CYP3A4 inhibitors: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of Amlodipine increased by 22 % and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of Amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.
- 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.

In clinical interaction studies grapefruit juice, cimetidine, aluminum/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of Amlodipine.
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, ethanol (alcohol), warfarin or cyclosporine.

There is no effect of Amlodipine on laboratory parameters.

ADVERSE EFFECTS
The following undesirable effects have been observed and reported during treatment with Amlodipine with the following frequencies: 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).
- Blood and the lymphatic system disorders: Leukocytopenia, thrombocytopenia (very rare).
- Immune system disorders: Allergic reactions (very rare).
- Metabolism and nutrition disorders: Hyperglycemia (very rare).
- Psychiatric disorders: Insomnia, mood changes (including anxiety), depression (uncommon); confusion (rare).
- Nervous system disorders: Somnolence, dizziness, headache (especially at the beginning of the treatment) (common); tremor, dysgeusia, syncope, hypoesthesia, paresthesia (uncommon); hypertonia, peripheral neuropathy (very rare).
- Eye disorders: Visual disturbance (including diplopia) (uncommon).
- Ear and labyrinth disorders: Tinnitus (uncommon).
- Cardiac disorders: Palpitations (uncommon); myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) (very rare).
- Vascular disorders: Flushing (common); hypotension (uncommon); vasculitis (very rare).
- Respiratory, thoracic and medicinal disorders: Dyspnea, rhinitis (uncommon); cough (very rare).
- Gastrointestinal disorders: Abdominal pain, nausea (common); vomiting, dyspepsia, altered bowel habits (including diarrhea and constipation), dry mouth (uncommon); pancreatitis, gastritis, gingival hyperplasia (very rare).
- Hepato-biliary disorders: Hepatitis, jaundice, increased hepatic enzymes (mostly consistent with cholestatis) (very rare).
- Skin and subcutaneous tissue disorders: Alopecia, purpura, skin discoloration, hyperhidrosis, pruritus, rash, exanthema (uncommon); angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke edema, photosensitivity (very rare).
- Musculoskeletal, connective tissue and bone disorders: Ankle swelling (common); arthralgia, myalgia, muscle cramps, back pain (uncommon).
- Renal and urinary disorders: Micturition disorder, nocturia, increased urinary frequency (uncommon).
- Reproductive system and breast disorders: Impotence, gynecomastia (uncommon).
- General disorders and administration site conditions: edema, fatigue (common); chest pain, asthenia, pain, malaise (uncommon).
- Investigations: Weight increase, weight decrease (uncommon).

DOSAGE AND ADMINISTRATION
For oral use.
The tablets should be taken with a glass of liquid (e.g. a glass of water) independently from meals.
Simultaneous intake of grapefruit or grapefruit juice has no influence on the effect of Amlodipine.
Adults
For the treatment of hypertension and angina pectoris, the usual dose is 5 mg Agen™ once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, the dose can be increased to a maximum dose of 10 mg daily (given as a single dose) depending on the individual response of the patient. Agen™ can be used as monotherapy or in combination with anti-anginal medication in patients suffering from angina pectoris.
Children with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in pediatric patients. The effect of Agen™ on blood pressure in patients less than 6 years of age is not known.
Elderly patients
For elderly patients, the normal dose is recommended; however, caution is advised when the dose is increased.
Patients with renal impairment
Agen™ may be used in such patients at normal doses. Changes in Agen™ plasma concentrations are not correlated with the degree of renal impairment. Agen™ is not dialyzable.
Patients with hepatic impairment
In patients with hepatic impairment, no dosage regimen has been defined; therefore Agen™ should be administered with caution.

OVERDOSAGE
In humans, experience with intentional overdose is limited.
Symptoms
Available data suggest that gross 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 have been reported.
Treatment
Clinically significant hypotension due to 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.
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.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of Amlodipine 10 mg has been shown to reduce the absorption rate of Amlodipine.
Since Amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

STORAGE CONDITIONS
Store below 25°C.
Keep in original pack in intact conditions.
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Manufactured by
Benta S.A.L., Dbayeh- Lebanon
BPI
Trademark owner ZENTIVA A SANOFI COMPANY

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Medicament: keep out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists