

## DATA SHEET

### **Arrow - Amlo 5 & Arrow - Amlo 10**

Amlodipine besilate 5 mg & 10 mg Tablets

#### **Presentation**

Arrow-Amlo 5 (5 mg tablets) are white to off white, round, biconvex, uncoated tablets.

Arrow-Amlo 10 (10 mg tablets) are white to off white, round, biconvex, uncoated tablets.

In addition to amlodipine besylate, each tablet contains the following inactive ingredients:

Calcium hydrogen phosphate dihydrate  
Microcrystalline cellulose  
Silica colloidal anhydrous  
Sodium starch glycollate  
Magnesium stearate

#### **Uses**

#### **Actions**

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine 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 (Prinzmetal's or variant angina) and blunts smoking induced coronary vasoconstriction.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. In patients with angina, once daily administration of amlodipine increases

total exercise time, time to angina onset and time to 1 mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

### **Use in Patients with Heart Failure**

Haemodynamic studies and exercise based controlled clinical trial in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology. A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA Class III-IV heart failure receiving digoxin, diuretics, and angiotensin converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk mortality or combined mortality and morbidity in patients with heart failure. In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis and diuretics, amlodipine has no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (Refer to "Warnings and Precautions"). Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

### **Pharmacokinetics**

Amlodipine is well absorbed orally with peak blood levels occurring 6-12 hours post-dose. Oral administration of a single therapeutic dose gave a mean absolute bioavailability of 64% (range 52-88%). The volume of distribution is approximately 20 L/kg. The absorption of amlodipine is unaffected by consumption of food. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive 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. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. Amlodipine is not dialysable.

### **Indications**

Amlodipine is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

Amlodipine is indicated for the first line treatment of myocardial ischaemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature.

Amlodipine may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine may be used alone as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or beta blockers.

### **Dosage and Administration**

For both hypertension and angina, the usual initial dose is 5 mg amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response. No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied. Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses.

Amlodipine is not recommended for use in children.

### **Contraindications**

Amlodipine tablets are contraindicated in patients with a known sensitivity to amlodipine, dihydropyridines or any of the inactive ingredients.

### **Warnings and Precautions**

In a long term placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of nonischaemic etiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (Refer to "USES-Use in Patients with Heart Failure"). Safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine did not demonstrate any foetotoxic or teratogenic potential in animal reproductive studies other than to delay parturition and prolong labor in rats at a dose level fifty times the maximum recommended dose in humans. No mutagenic activity has been found in tests for gene mutations or cytogenic assays. Accordingly, use in pregnancy is recommended only when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus. As with all calcium channel blockers, amlodipine half-life is prolonged in patients with impaired liver function and dosage

recommendations have not been established. The compound should therefore be administered with caution in these patients. Safety and effectiveness of amlodipine in children have not been established. Clinical experience with amlodipine indicates that it is unlikely to impair a patient's ability to drive.

### **Adverse Effects**

Amlodipine is well-tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were headache, edema, fatigue, somnolence, nausea, abdominal pain, flushing, palpitations and dizziness. In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed. Less commonly observed side effects in marketing experience include:

**Autonomic Nervous:** dry mouth, increased sweating

**Body As A Whole:** asthenia, back pain, malaise, pain, weight increase/decrease

**Cardiovascular, General:** hypotension, syncope

**Central & Peripheral Nervous:** hypertonia, hypoesthesia/paresthesia, peripheral neuropathy, tremor

**Endocrine:** gynaecomastia

**Gastrointestinal:** altered bowel habits, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting

**Metabolic/Nutritional:** hyperglycaemia

**Musculoskeletal:** arthralgia, muscle cramps, myalgia

**Platelet/Bleeding/Clotting:** purpura, thrombocytopenia

**Psychiatric:** impotence, insomnia, mood changes

**Respiratory:** coughing, dyspnoea, rhinitis

**Skin/Appendages:** alopecia, skin discoloration, urticaria

**Special senses:** taste perversion, tinnitus

**Urinary:** increased urinary frequency, micturition disorder, nocturia

**Vascular (Extracardiac):** vasculitis

Vision: visual disturbances

White Blood Cell/R.E.S.: leucopenia

Rarely, allergic reactions including pruritis, rash, angioedema and erythema multiforme have been reported.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

## Interactions

Amlodipine has been safely administered with thiazide diuretics, beta blockers, alpha blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory agents, antibiotics, and oral hypoglycaemic agents. *In vitro* data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

### Special Studies: Effect of other agents on amlodipine

*Cimetidine*: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

*Grapefruit Juice*: Co-administration of 240mL of grapefruit juice with a single oral dose of amlodipine 10mg in 20 health volunteers had no significant effect on the pharmacokinetics of amlodipine.

*Aluminium/Magnesium (antacid)*: Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

*Sildenafil*: A single 100mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetics parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

### Special Studies: Effect of amlodipine on other agents

*Atorvastatin*: Co-administration of multiple 10mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

*Digoxin*: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

*Ethanol (alcohol)*: Single and multiple 10mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

*Warfarin*: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

*Cyclosporin*: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

## Overdosage

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to an including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. 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. Dialysis is not likely to be of benefit since amlodipine is highly protein-bound.

### **Pharmaceutical Precautions**

Do not store above 25°C.

Store in the original package.

### **Medicine Classification**

Prescription Medicine

### **Package Quantities**

**Arrow-Amlo 5 (5 mg Tablets):** Blister packs containing 28, 56 or 84 tablets and HDPE containers containing 100, 250 or 500 tablets.

**Arrow-Amlo 10 (10 mg Tablets):** Blister packs containing 28, 56 or 84 tablets and HDPE containers containing 100, 250 or 500 tablets.

Not all pack sizes may be marketed

### **Further Information**

Amlodipine besylate is a dihydropyridine derivative, and has the following chemical name:

3-ethyl 5-methyl 2- (2-aminoethoxymethyl)-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate benzenesulphonate.

Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol, and has a molecular weight of 567.1 (free base 408.9).

### **Name and Address**

#### **Sponsor**

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#### **Date of Preparation**

14 February 2011