

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

RUSTIN 10 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Amlodipine Besilate equivalent to 10 mg Amlodipine.

For full list of excipients see section 6.1

### 3 PHARMACEUTICAL FORM

Tablet

White, round, slightly arched tablets, with “AB 10” and breakline on one side and plain on the other. The tablet can be divided into equal halves.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

1. In the management of essential hypertension and be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive may benefit from the addition of Rustin, which has been used in combination with a thiazide diuretic, alpha-blocker, beta-adrenoceptor blocking agent, or an angiotensin-converting enzyme inhibitor.
2. In the prophylaxis of angina pectoris associated with myocardial ischaemia whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal or variant angina) of the coronary vasculature.
3. It may also be used where the clinical presentation suggests a possible vasospastic/vasoconstriction component but where vasospasm/vasoconstriction has not been confirmed.
4. It may be used as monotherapy, or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta-adrenoceptor blocking agents.
5. Rustin is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

#### 4.2 Posology and method of administration

In Adults: For both hypertension and angina, the usual initial dose is 5mg amlodipine once daily which may be increased to a maximum dose of 10mg 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.

In children: Not recommended

Use in Elderly: Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with Renal Impairment: Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment therefore the normal dosage is recommended.

Patients with Hepatic Impairment: See section 4.4, Special warnings and precautions for use.

### 4.3 Contraindications

Patients with a known hypersensitivity to dihydropyridines.  
Hypersensitivity to amlodipine or to any of the excipients.

### 4.4 Special warnings and precautions for use

**Use in patients with Heart Failure:** In a long-term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1, Pharmacodynamic properties.

**Use in patients with Hepatic Impairment:** As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.  
See section 4.8, Undesirable Effects.

### 4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, alpha-blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

Amlodipine will not protect against the effects of withdrawal of  $\beta$ -adrenoceptor blocking agents, nor the rebound effects seen with various hypertensive agents.

#### **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 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

**Aluminium/magnesium (antacid):** Co-administration of 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 pharmacokinetic 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.

**Drug/Laboratory test interactions:** None known.

### 4.6 Fertility, pregnancy and lactation

Studies in animals do not suggest a teratogenic effect, although the drug crosses the placenta readily. It is also excreted in breast milk. There is no experience of use during pregnancy in human beings.

The product should only be used during pregnancy if considered essential, and should be avoided in women who are breast feeding.

4.7 Effects on ability to drive and use machines

Clinical experience with Rustin indicates that it is unlikely to impair a patient’s ability to drive or use machinery, however see section 4.8, Undesirable effects.

4.8 Undesirable effects

Adverse events that have been reported in amlodipine trials are categorised below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (>0.01%).

|                                                 |                                                                                                            |           |
|-------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------|
| Blood and the Lymphatic System disorders        | Thrombocytopenia, leucopenia                                                                               | Very rare |
| Immune System disorders                         | Allergic reactions                                                                                         | Very rare |
| Metabolism and Nutrition disorders              | Hyperglycaemia                                                                                             | Very rare |
| Psychiatric disorders                           | Insomnia, mood changes                                                                                     | Uncommon  |
| Nervous System disorders                        | Somnolence, dizziness, headache                                                                            | Common    |
|                                                 | Tremor, taste perversion, syncope, hypoaesthesia, paraesthesia                                             | Uncommon  |
|                                                 | Hypertonia, peripheral neuropathy                                                                          | Very rare |
| Eye disorders                                   | Visual disturbances                                                                                        | Uncommon  |
| Ear and Labyrinth disorders                     | Tinnitus                                                                                                   | Uncommon  |
| Cardiac disorders                               | Palpitations                                                                                               | Common    |
|                                                 | Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) | Very rare |
| Vascular disorders                              | Flushing                                                                                                   | Common    |
|                                                 | Hypotension                                                                                                | Uncommon  |
|                                                 | Vasculitis                                                                                                 | Very rare |
| Respiratory, Thoracic and Mediastinal disorders | Dyspnoea, rhinitis                                                                                         | Uncommon  |
|                                                 | Coughing                                                                                                   | Very rare |

|                                                      |                                                                                       |           |
|------------------------------------------------------|---------------------------------------------------------------------------------------|-----------|
| Gastrointestinal disorders                           | Abdominal pain, nausea                                                                | Common    |
|                                                      | Vomiting, dyspepsia, altered bowel habits, dry mouth                                  | Uncommon  |
|                                                      | Pancreatitis, gastritis, gingival hyperplasia                                         | Very rare |
| Hepato-biliary disorders                             | Hepatitis, jaundice and hepatic enzyme elevation (mostly consistent with cholestasis) | Very rare |
| Skin and Subcutaneous Tissue disorders               | Alopecia, purpura, skin discolouration, increased sweating, pruritus, rash            | Uncommon  |
|                                                      | Angioedema, erythema multiforme, urticaria                                            | Very rare |
| Musculoskeletal and Connective Tissue disorders      | Arthralgia, myalgia, muscle cramps, back pain                                         | Uncommon  |
| Renal and Urinary disorders                          | Micturition disorders, nocturia, increased urinary frequency                          | Uncommon  |
| Reproductive System and Breast disorders             | Impotence, gynaecomastia                                                              | Uncommon  |
| General disorders and Administration Site conditions | Oedema, fatigue                                                                       | Common    |
|                                                      | Chest pain, asthenia, pain, malaise                                                   | Uncommon  |
| Investigations                                       | Weight increase, weight decrease                                                      | Uncommon  |

Very rarely, heart block has been found in patients treated with amlodipine and causality is uncertain.

## 4.9 Overdose

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage could result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension.

Clinically significant hypotension due to Rustin overdosage calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure, provided that there is no contra-indication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since Rustin is highly protein-bound, dialysis is unlikely to be of benefit.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:**

Selective calcium channel blockers with mainly vascular effects

**ATC Code:** C08CA01

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 vascular smooth muscle.

The mechanism of the antihypertensive action of Rustin is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which Rustin relieves angina has not been fully determined but Rustin reduces total ischaemic burden by the following two actions:

1. 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.
2. The mechanism of action of Rustin probably involves dilation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal or variant angina).

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 treatment.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

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.

**Use in Patients with Heart Failure:**

Haemodynamic studies and exercise based controlled clinical trials 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 in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity 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 or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had 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.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98, 95% CI [0.90-1.07] p=0.65.

Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy, RR 0.96, 95% CI [0.89-1.02] p=0.20.

## 5.2 Pharmacokinetic properties

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 21L/kg. 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 to inactive metabolites with 0% of the parent compound and 60% of metabolites excreted in the urine.

## 5.3 Preclinical safety data

None stated

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Microcrystalline cellulose  
Calcium hydrogen phosphate, anhydrous  
Sodium starch glycollate  
Magnesium stearate

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

5 Years

## 6.4 Special precautions for storage

Do not store above 30°C.

## **6.5 Nature and contents of container**

*Aluminium foil:*

Al 20 µm thick

*Plastic:*

PVC/PVdC white opaque foil containing 20, 28, 28 calendar pack, 30, 30 (3 x 10), 50, 56, 84, 100, 300 (3 x 100) tablets.

Not all pack sizes may be marketed

## **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements

## **7 MARKETING AUTHORISATION HOLDER**

Ergha Healthcare Ltd.

Damastown

Mulhuddart

Dublin 15

## **8 MARKETING AUTHORISATION NUMBER**

PA 966/10/2

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 12<sup>th</sup> January 2007

Date of Last Renewal: 12<sup>th</sup> January 2012

## **10 DATE OF REVISION OF THE TEXT**

August 2012