Public Assessment Report

Decentralised Procedure

Amlodipine 5 mg Tablets
Amlodipine 10 mg Tablets

Procedure No: UK/H/4730/001-2/DC

UK Licence No: PL 00289/1558-9

Teva UK Limited
Lay summary

On 25 January 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Teva UK Limited for the medicinal products Amlodipine 5 mg and 10 mg Tablets (PL 00289/1558-9; UK/H/4730/001-2/DC). These are prescription-only medicines (POM) used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, including the rare form Printzmetal’s (or variant) angina. Amlodipine Tablets do not provide immediate relief of chest pain from angina.

Amlodipine Tablets contain the active ingredient amlodipine (as amlodipine besilate). Amlodipine belongs to a group of medicines called calcium channel blockers. In patients with high blood pressure, amlodipine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina, amlodipine works by improving blood supply to the heart muscle, which then receives more oxygen and, as a result, chest pain is prevented.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amlodipine 5 mg and 10 mg Tablets; outweigh the risks; hence Marketing Authorisations were granted.
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## Module 1
### Information about the initial procedure

| **Product Names** | UK/H/4730/001/DC: Amlodipine 5 mg Tablets  
                    UK/H/4730/002/DC: Amlodipine 20 mg Tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Applications</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Amlodipine besilate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strengths</strong></td>
<td>5 mg and 10 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Germany, Spain, Italy, the Netherlands, Portugal and Romania</td>
</tr>
<tr>
<td><strong>Procedure Numbers</strong></td>
<td>UK/H/4730/001-2/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 11 January 2012</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg amlodipine (as besilate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White, round, slightly arched tablets, 8 mm in diameter and 3.3 – 4.1 mm thick, debossed AB 5 on one side, plain on the other side

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension.
Chronic stable angina pectoris.
Vasospastic (Prinzmetal’s) angina

4.2 Posology and method of administration
For oral use

Posology
Adults
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.

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations
Elderly
Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.
Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age

The recommended antihypertensive oral dose in paediatric 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 paediatric patients (see sections 5.1 and 5.2).

Doses of amlodipine 2.5 mg are not possible with this medicinal product.

Children under 6 years old
No data are available.

4.3 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)
- haemodynamically unstable heart failure after acute myocardial infarction

4.4 Special warnings and precautions for use
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 oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). 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.

Use in patients with impaired hepatic function
The half life of amlodipine 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. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in elderly patients
In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction
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 the elderly. 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 (e.g. 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 hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, 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 medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

4.6 Fertility, Pregnancy and lactation

Pregnancy
The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding
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.

Fertility
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on 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. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects
The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1000 and <1/100); rare (≥1/10 000 and <1/1000); very rare (<1/10 000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very rare</td>
<td>Leukocytopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very rare</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Insomnia, mood changes (including anxiety), depression</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Confusion</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Undesirable Effects</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Common</td>
<td>Somnolence, dizziness, headache (especially at the beginning of the treatment)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tremor, dysgeusia, syncope, hypoesthesia, paresthesia</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Hypertonia, peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Uncommon</td>
<td>Visual disturbance (including diplopia)</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Common</td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Common</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Vasculitis</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and medicinal disorders</strong></td>
<td>Uncommon</td>
<td>Dyspnoea, rhinitis</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Cough</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Common</td>
<td>Abdominal pain, nausea</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vomiting, dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Pancreatitis, gastritis, gingival hyperplasia</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Very Rare</td>
<td>Hepatitis, jaundice, hepatic enzymes increased *</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Uncommon</td>
<td>Alopecia, purpura, skin discoulouration, hyperhydrosis, pruritus, rash, exanthema</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Angioedema, erythema multiforme, urticaaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective</strong></td>
<td>Common</td>
<td>Ankle swelling</td>
</tr>
</tbody>
</table>
Amlodipine 5 mg and 10 mg Tablets

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>tissue disorders</td>
<td>Uncommon</td>
<td>Arthralgia, myalgia, muscle cramps, back pain</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon</td>
<td>Micturition disorder, nocturia, increased urinary frequency</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>Impotence, gynecomastia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Oedema, fatigue</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Chest pain, asthenia, pain malaise</td>
</tr>
<tr>
<td>Investigations</td>
<td>Uncommon</td>
<td>Weight increase, weight decrease</td>
</tr>
</tbody>
</table>

*mostly consistent with cholestatis

Exceptional cases of extrapyramidal syndrome have been reported.

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC code: C08CA01.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into the cardiac and vascular 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:

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 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).

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 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 coronary artery disease (CAD)

<table>
<thead>
<tr>
<th>Table 1. Incidence of significant clinical outcomes for CAMELOT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular event rates, No. (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
</tr>
<tr>
<td>Adverse cardiovascular events</td>
<td>110 (16.6)</td>
</tr>
<tr>
<td>Individual Components</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>78 (11.8)</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>51 (7.7)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14 (2.1)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>0</td>
</tr>
<tr>
<td>New-onset peripheral vascular disease</td>
<td>5 (0.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Use in Patients with Heart Failure
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class III-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 of 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.

**Treatment to prevent heart attack trial (ALLHAT)**
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.

**Use in children (aged 6 years and older)**
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

### 5.2 Pharmacokinetic properties

**Absorption, distribution, plasma protein binding:** 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 bioavailability of amlodipine is not affected by food intake.

**Biotransformation/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 into inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

**Use in hepatic impairment**
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

**Use in the Elderly**  
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.

**Use in Children**  
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

### 5.3 Preclinical safety data

**Reproductive toxicology**  
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

**Impairment of fertility**  
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

**Carcinogenesis, mutagenesis**  
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Microcrystalline cellulose
- Calcium hydrogen phosphate, anhydrous
- Sodium starch glycolate (type A)
- Magnesium stearate

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

5 years

#### 6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light and moisture. Keep the blister in the outer carton.
6.5 Nature and contents of container
White opaque PVC/PVdC-aluminium blister in cardboard boxes

Pack sizes: 15, 20, 28, 30, 30 (3 x 10), 50, 56, 84, 90, 98, 100, 112 and 300 (10 x 30) tablets.
Calendar packs: 28
Hospital pack: 50

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG,
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1558

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/01/2012

10 DATE OF REVISION OF THE TEXT
25/01/2012
1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg amlodipine (as besilate)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White, round, slightly arched tablets, 11 mm in diameter and 3.8 – 4.6 mm thick debossed AB 10 and breakline on one side, plain on the order side

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension.
Chronic stable angina pectoris.
Vasospastic (Prinzmetal’s) angina

4.2 Posology and method of administration
For oral use

Posology
Adults
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.

In hypertensive patients, amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

Elderly
Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric 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 paediatric patients (see sections 5.1 and 5.2).
Doses of amlodipine 2.5 mg are not possible with this medicinal product.

Children under 6 years old
No data are available.

4.3 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)
- haemodynamically unstable heart failure after acute myocardial infarction

4.4 Special warnings and precautions for use
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 oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). 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.

Use in patients with impaired hepatic function
The half life of amlodipine 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. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in elderly patients
In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 the elderly. 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 (e.g. 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 hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, 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 medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

4.6 Fertility, Pregnancy and lactation

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

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.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on 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. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1000 and <1/100); rare (≥1/10000 and <1/1000); very rare (<1/10 000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very rare</td>
<td>Leukocytopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very rare</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Insomnia, mood changes (including anxiety), depression</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Confusion</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Somnolence, dizziness, headache (especially at the beginning of the treatment)</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Undesirable Effects</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tremor, dysgeusia, syncope, hypoesthesia, paresthesia</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Hypertonia, peripheral neuropathy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Visual disturbance (including diplopia)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and medicinal disorders</td>
<td>Uncommon</td>
<td>Dyspnoea, rhinitis</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Abdominal pain, nausea</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vomiting dyspepsia, altered bowel habits (including diarrhoea and constipation), dry mouth</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Pancreatitis, gastritis, gingival hyperplasia</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very Rare</td>
<td>Hepatitis, jaundice, hepatic enzymes increased *</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, rash, exanthema</td>
</tr>
<tr>
<td></td>
<td>Very Rare</td>
<td>Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity</td>
</tr>
</tbody>
</table>
**System Organ Class** | **Frequency** | **Undesirable Effects**
--- | --- | ---
**Musculoskeletal and connective tissue disorders** | Common | Ankle swelling
 | Uncommon | Arthralgia, myalgia, muscle cramps, back pain

**Renal and urinary disorders** | Uncommon | Micturition disorder, nocturia, increased urinary frequency

**Reproductive system and breast disorders** | Uncommon | Impotence, gynecomastia

**General disorders and administration site conditions** | Common | Oedema, fatigue
 | Uncommon | Chest pain, asthenia, pain malaise

**Investigations** | Uncommon | Weight increase, weight decrease

*mostly consistent with cholestatis

Exceptional cases of extrapyramidal syndrome have been reported.

### 4.9 Overdose

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.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC code: C08CA01.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into the cardiac and vascular 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:

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 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).

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 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 coronary artery disease (CAD)

<table>
<thead>
<tr>
<th>Table 1. Incidence of significant clinical outcomes for CAMELOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Primary Endpoint</td>
</tr>
<tr>
<td>Adverse cardiovascular events</td>
</tr>
<tr>
<td>Individual Components</td>
</tr>
<tr>
<td>Coronary revascularization</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
</tr>
<tr>
<td>Nonfatal MI</td>
</tr>
<tr>
<td>Stroke or TIA</td>
</tr>
<tr>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
</tr>
<tr>
<td>New-onset peripheral vascular disease</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.
Use in Patients with Heart Failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class III-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 of 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.

**Treatment to prevent heart attack trial (ALLHAT)**

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.

**Use in children (aged 6 years and older)**

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

### 5.2 Pharmacokinetic properties

**Absorption, distribution, plasma protein binding:** 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 bioavailability of amlodipine is not affected by food intake.

**Biotransformation/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 into inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Use in hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Use in the Elderly
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.

Use in Children
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3 Preclinical safety data
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Microcrystalline cellulose
Calcium hydrogen phosphate, anhydrous
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years

6.4 Special precautions for storage
Do not store above 25°C.

Store in the original package in order to protect from light and moisture. Keep the blister in the outer carton.
6.5 Nature and contents of container
White opaque PVC/PVdC-aluminium blister in cardboard boxes

Pack sizes: 14, 15, 20, 28, 30, 30 (3 x 10), 50, 56, 84, 90, 98, 100 and 112 tablets.
Calendar packs: 28
Hospital pack: 50

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited,
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG,
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1559

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/01/2012

10 DATE OF REVISION OF THE TEXT
25/01/2012
Module 3

The leaflet text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder is required to submit the mock-up leaflet to the relevant regulatory authorities before marketing any pack size in a particular member state.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Amlodipine 5 mg and 10 mg Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:
1. What Amlodipine Tablets are and what they are used for
2. Before you take Amlodipine Tablets
3. How to take Amlodipine Tablets
4. Possible side effects
5. How to store Amlodipine Tablets
6. Further information

1. WHAT AMLODIPINE TABLETS ARE AND WHAT THEY ARE USED FOR

Amlodipine Tablets contain the active substance amlodipine (as besilate) which belongs to a group of medicines called calcium antagonists.

Amlodipine Tablets are used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal’s or variant angina.

In patients with high blood pressure your medicine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina Amlodipine Tablets work by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Your medicine does not provide immediate relief of chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE TABLETS

Do not take Amlodipine Tablets:
- If you are allergic (hypersensitive) to amlodipine, or any of the other ingredients of your medicine listed in section 6, or to any other calcium antagonists. This may be itching, reddening of the skin or difficulty in breathing.
- If you have severe low blood pressure (hypotension)
- If you have a narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack

Take special care with Amlodipine Tablets:
You should inform your doctor if you have or have had any of the following conditions:
- Recent heart attack
- Heart failure
- Severe increase in blood pressure (Hypertensive crisis)
- Liver disease
- You are elderly and your dose needs to be increased
Use in children and adolescents
Amlodipine has not been studied in children under the age of 6 years. Amlodipine Tablets should only be used for hypertension in children and adolescents from 6 years to 17 years of age (see section 3). For more information, talk to your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Amlodipine Tablets may be affected by other medicines such as:
- ketoconazole and itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nelfinavir (so-called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics)
- hypericum perforatum (St. John's Wort)
- verapamil, diltiazem (heart medicines)
- dantrolene (infusion for severe body temperature abnormalities)

Amlodipine Tablets may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

Taking Amlodipine Tablets with food and drink
Grapefruit juice and grapefruit should not be consumed by people who are taking Amlodipine Tablets. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Amlodipine Tablets.

Pregnancy
The safety of amlodipine in human pregnancy has not been established. If you think you might be pregnant, or are planning to get pregnant, you must tell your doctor before you take Amlodipine Tablets.

Breast-feeding
It is not known whether amlodipine is passed into breast milk. If you are breast-feeding or about to start breast-feeding you must tell your doctor before taking Amlodipine Tablets.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Amlodipine Tablets may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

3. **HOW TO TAKE AMLODIPINE TABLETS**

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual initial dose is one Amlodipine 5 mg Tablet, once daily. The dose can be increased to one Amlodipine 10 mg Tablet once daily.

Your medicine can be used before or after food and drinks. You should take your medicine at the same time each day with a drink of water. Do not take Amlodipine Tablets with grapefruit juice.
Use in children and adolescents
For children and adolescents (6-17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day. Amlodipine 2.5 mg Tablets are not currently available and the 2.5 mg dose cannot be obtained with Amlodipine 5 mg Tablets as these tablets are not manufactured to break into two equal halves.

It is important to keep taking the tablets. Do not wait until your tablets are finished before seeing your doctor.

If you take more Amlodipine Tablets than you should
Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Amlodipine Tablets.

If you forget to take Amlodipine Tablets
Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a missed dose.

If you stop taking Amlodipine Tablets
Your doctor will advise you how long to take your medicine. Your condition may return if you stop using your medicine before you are advised.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Amlodipine Tablets can cause side effects, although not everybody gets them.

Visit your doctor immediately if you experience any of the following very rare, severe side effects after taking this medicine.

- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty breathing
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens-Johnson Syndrome) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

The following common side-effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Common affects 1 to 10 users in 100
- Headache, dizziness, sleepiness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Ankle swelling (oedema), tiredness

Other side-effects that have been reported include the following list. If any of these get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.
Uncommon: affects 1 to 10 users in 1,000
- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, foaming, weakness
- Numbness or tingling sensation in your limbs; loss of pain sensation
- Visual disturbances, double vision, ringing in the ears
- Low blood pressure
- Sneezing/runny nose caused by inflammation of the lining of the nose (rhinitis)
- Altered bowel habits, diarrhoea, constipation, indigestion, dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection; discomfort or enlargement of the breasts in men
- Weakness, pain, feeling unwell
- Joint or muscle pain, muscle cramps, back pain
- Weight increase or decrease

Rare: affects 1 to 10 users in 10,000
- Confusion

Very rare: affects less than 1 user in 10,000
- Decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage)
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause weakness, tingling or numbness
- Cough, swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE AMLODIPINE TABLETS

Keep out of the reach and sight of children.

Do not use your medicine after the expiry date stated on the blisters and outer packaging. The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original packaging in order to protect from light and moisture. Keep the blister in the outer carton. Do not take these tablets if there are any signs of discolouration or deterioration of the tablets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. FURTHER INFORMATION

What Amlodipine Tablets contain

- The active ingredient is amlodipine (as besilate).
  Each 5 mg tablet contains amlodipine besilate equivalent to 5 mg amlodipine.
  Each 10 mg tablet contains amlodipine besilate equivalent to 10 mg amlodipine.
- The other ingredients are microcrystalline cellulose, calcium hydrogen phosphate, sodium starch
  glycollate and magnesium stearate.

What Amlodipine Tablets look like and contents of the pack:

- Amlodipine 5 mg Tablets are white, round, slightly arched tablets debossed AB 5 on one side, plain on
  the other side. packed in blisters and available in pack sizes of 15, 20, 28, 30, 50, 64, 90, 98, 100,
  112 and 300 tablets
- Amlodipine 10 mg Tablets are white, round, slightly arched tablets, debossed AB 10 and breakline on
  one side, plain on the other side, packed in blisters and available in pack sizes of 14, 15, 20, 28, 30, 50,
  56, 84, 90, 98, 100 and 112 tablets. The breakline is only to facilitate breaking for ease of swallowing
  and not to divide into equal doses.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Teva UK Limited, Eastbourne, BN22 9AG, UK

Manufacturer
TEVA Pharmaceutical Works Private Limited Company
Pallagi ut 13, 4042 Debrecen,
Hungary

Or:
TEVA Pharmaceutical Works Private Limited Company
H-2100 Godollo, Táncsics Mihaly ut 82,
Hungary

Or:
TEVA UK Ltd
Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG
UK

Or:
Pharmachemie B.V.
Swensweg 5, 2031 GA Haarlem
The Netherlands

Or:
TEVA Santé
Rue Bellozier, 89100 Seas
France

Or:
Teva Czech Industries s.r.o.
Osraviska 29, c.p. 305, 74770 Opatov-Komarov
Czech Republic

Or:
Merckle GmbH
Ludwig-Merckle-Straße 3, 89143 Blaubeuren
Germany

This leaflet was last revised in January 2012.

PL 00289/1558
PL 00289/1559
Module 4

The labelling text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder is required to submit the mock-up labelling to the relevant regulatory authorities before marketing any pack size in a particular member state.

For PL 00289/1558:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of amlodipine (as besilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

15 tablets
20 tablets
28 tablets
30 tablets
30 (3 x 10) tablets
50 tablets
50 tablets
84 tablets
90 tablets
98 tablets
100 tablets
112 tablets
300 (10 x 30) tablets
Calendar packs: 28
Hospital pack: 50 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

To be used as directed by a medical practitioner.

Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original packaging in order to protect from light and moisture.
Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
Teva UK Ltd, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)
PL 00289/1558

13. BATCH NUMBER
LOT

14. GENERAL CLASSIFICATION FOR SUPPLY
POM

15. INSTRUCTIONS ON USE
Use as directed by the doctor

16. INFORMATION IN BRAILLE
Amlodipine 5 mg Tablets
### Minimum particulars to appear on blisters or strips

<table>
<thead>
<tr>
<th>BLISTER</th>
</tr>
</thead>
</table>

1. **Name of the medicinal product**

   Amlodipine 5 mg Tablets

2. **Name of the marketing authorisation holder**

   Teva UK Ltd

3. **Expiry date**

   EXP

4. **Batch number**

   LOT

5. **Other**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of amlodipine (as besilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 tablets
15 tablets
20 tablets
28 tablets
30 tablets
30 (3 x 10) tablets
50 tablets
56 tablets
84 tablets
90 tablets
98 tablets
100 tablets
112 tablets
Calendar packs: 28 tablets
Hospital pack: 50 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

To be used as directed by a medical practitioner.

Please read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original packaging in order to protect from light and moisture.
Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1559

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Amlodipine 10 mg Tablets
Amlodipine 5 mg and 10 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER
Module 5
Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Amlodipine 5 mg and 10 mg Tablets (PL 00289/1558-9; UK/H/4730/001-2/DC) could be approved. The products are prescription-only medicines for the treatment of:

- hypertension (high blood pressure)
- chronic stable angina pectoris
- vasospastic (Prinzmetal's) angina.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Spain, Italy, the Netherlands, Portugal and Romania as Concerned Member States (CMS). These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal product for these applications is Norvasc 10mg Tablets (Pfizer Limited, the Netherlands), which was first authorised in the Netherlands on 03 June 1990. Reference is also made to the corresponding UK reference products Istin 5 mg and 10 mg Tablets (Pfizer Limited, UK), which were first authorised in the UK on 18 September 1989.

The active ingredient amlodipine (as amlodipine besilate) is a dihydropyridine calcium ion influx inhibitor (slow channel blocker). It inhibits the transmembrane influx of calcium ions into cardiac and smooth muscle cells.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Amlodipine 10 mg Tablets (Teva UK Limited, UK) versus the reference products Istin 10 mg Tablets (Pfizer Limited, UK) and Norvasc 10 mg Tablets (Pfizer SA, Belgium). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 11 January 2012. After a subsequent national phase, licences were granted in the UK on 25 January 2012.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | UK/H/4730/001/DC: Amlodipine 5 mg Tablets  
UK/H/4730/002/DC: Amlodipine 10 mg Tablets |
<table>
<thead>
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<tbody>
<tr>
<td>Name(s) of the active substance (INN)</td>
<td>Amlodipine besilate</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code)  | Calcium channel blockers, selective calcium channel blockers with mainly vascular effects.  
(ATC code: C08CA01) |
| Pharmaceutical form and strength(s)           | Tablets  
5 mg and 10 mg                                                                 |
| Reference numbers for the Decentralised Procedure | UK/H/4730/001-2/DC                                                                |
| Reference Member State (RMS)                   | United Kingdom                                                                    |
| Concerned Member States (CMS)                  | Germany, Spain, Italy, the Netherlands, Portugal and Romania                      |
| Marketing Authorisation Number(s)              | PL 00289/1558-9                                                                  |
| Name and address of the authorisation holder   | Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Amlodipine besilate
Chemical Name: 3-Ethyl 5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.

Molecular Formula: $C_{20}H_{25}ClN_2O_5$, $C_6H_6O_3S$

Structure

Molecular weight: 567.1 g/mol
Appearance: A white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in 2-propanol.

Amlodipine besilate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance amlodipine besilate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, anhydrous calcium hydrogen phosphate, sodium starch glycolate (type A) and magnesium stearate. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Istin 5 mg and 10 mg Tablets (Pfizer Limited, UK), and the corresponding EU reference Norvasc products in Germany, Denmark, Spain, Italy, the Netherlands and Norway.

Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution and impurity profiles have been provided for these products and their respective reference products.
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packaged in white opaque polyvinylchloride/polvinylidene chloride/aluminium blisters in pack sizes of 14 (10 mg strength tablet only) 15, 20, 28, 28 (calendar packs), 30, 30 (3 x 10), 50, 50 (hospital packs), 56, 84, 90, 98, 100, 112 and 300 (10 x 30) (5 mg strength tablet only) tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years years has been proposed, with the storage conditions “Do not store above 25°C. Store in the original package in order to protect from light and moisture. Keep the blister in the outer carton.”

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
**MAA Forms**
All aspects of the MAA forms are pharmaceutically satisfactory.

**Expert Report**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine besilate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS
The clinical pharmacology of amlodipine besilate is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, open label, single-dose, three-way, three-period, crossover study comparing the pharmacokinetics of the test product Amlodipine 10 mg Tablets (Teva UK Limited, UK) and the reference products Istin 10 mg (Pfizer Limited, UK) and Norvasc 10 mg Tablets (Pfizer SA, Belgium) in healthy adult male and female subjects under fasting conditions.

The subjects were given a single dose of one 10 mg tablet of the test or reference product after at least a 10 hour overnight fast. Blood samples were collected within 2 hours before and up to 216 hours after each administration. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below.

| Pharmacokinetic parameters (arithmetic mean±SD) of amlodipine besilate |
|--------------------------|--------------------------|--------------------------|
| Parameters | Amlodipine 10 mg (Test, (A)) | Istin 10 mg (Reference 1, (B)) | Norvasc 10 mg (Reference 2, (C)) |
| AUC_{0-t} (pg h/mL) | 311630.87±67172.23 | 307124.40±65048.90 | 303998.80±72046.50 |
| AUC_{0-inf} (pg h/mL) | 325404.01±74174.68 | 320424.24±68348.01 | 318587.92±75201.97 |
| C_{max} (pg/mL) | 6249.29±1187.41 | 6099.79±1185.03 | 5934.25±1272.01 |

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
SD=standard deviation

<table>
<thead>
<tr>
<th>Treatment comparisions</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (pg h/mL)</td>
<td>Amlodipine (A) vs. Istin (B)</td>
<td>101.49</td>
<td>97.22-105.95</td>
</tr>
<tr>
<td></td>
<td>Amlodipine (A) vs. Norvasc (C)</td>
<td>103.24</td>
<td>98.89-107.78</td>
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<tr>
<td>AUC_{0-inf} (pg h/mL)</td>
<td>Amlodipine (A) vs. Istin (B)</td>
<td>101.36</td>
<td>96.86-106.07</td>
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<tr>
<td></td>
<td>Amlodipine (A) vs. Norvasc (C)</td>
<td>102.60</td>
<td>98.04-107.37</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>Amlodipine (A) vs. Istin (B)</td>
<td>102.32</td>
<td>97.80-107.05</td>
</tr>
<tr>
<td></td>
<td>Amlodipine (A) vs. Norvasc (C)</td>
<td>105.72</td>
<td>101.05-110.61</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
Ratios and 90% CI calculated from log-transformed data

The *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80% to 125% for C_{max} and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC_{0-t}, AUC_{0-inf} and C_{max} lie within the acceptable limits. Thus, the data support the claim that the test product Amlodipine 10 mg Tablets (Teva UK Limited, UK) is bioequivalent to the reference products Istin 10 mg Tablets (Pfizer Limited, UK) and Norvasc 10 mg Tablets (Pfizer SA, Belgium).
As the 5 mg and 10 mg strengths of the product meet all the criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1), for (bio) waiver, the results and conclusions from the bioequivalence study with the 10 mg tablet strength can be extrapolated to the 5 mg tablet strength.

**EFFICACY**

The efficacy of amlodipine besilate is well-known. No new efficacy data have been submitted and none are required for applications of this type.

**SAFETY**

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

**PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**

The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

**CLINICAL EXPERT REPORT**

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**CONCLUSION**

The grant of Marketing Authorisations is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The quality characteristics of Amlodipine 5 mg and 10 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of amlodipine besilate are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 10mg strength tablets and its reference product. As the 5mg and 10mg strengths of the product meet the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), the results and conclusions from the bioequivalence study with the 10mg tablet strength can be extrapolated to the 5mg tablet strength.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of amlodipine besilate is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amlodipine besilate is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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