AMLODIPINE 5MG TABLETS
AMLODIPINE 10MG TABLETS

UKPAR

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AMLODIPINE 5MG TABLETS
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LAY SUMMARY

The MHRA granted Wockhardt UK Limited Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg and 10mg Tablets on 29th September 2009. These products, available by prescription only (POM), are used to treat high blood pressure and chest pain due to narrowing of the coronary arteries of the heart muscle (angina pectoris) or the more rare form of chest pain caused by cramping of the coronary arteries of the heart muscle (vasoplastic angina).

The active ingredient amlodipine besilate belongs to a group of medicines called calcium antagonists. If you suffer from high blood pressure, amlodipine works by relaxing blood vessels so that blood passes through them more easily. If you suffer from angina, amlodipine works by improving the blood supply to the heart muscle, which then receives more oxygen and as a result chest pain is prevented. Amlodipine does not provide immediate relief from chest pain.

These applications are the same as previously granted applications for Amlodipine 5mg and 10mg Tablets (PL 19156/0033 and 0034), which were originally approved in May 2007 to Jubilant Pharmaceuticals BV.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Amlodipine 5mg and 10mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
AMLODIPINE 5MG TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Amlodipine 5mg and 10mg Tablets (PL 29831/0451-2) to Wockhardt UK Limited on 29th September 2009. The products are available as a prescription-only medicines (POM) for essential hypertension, and chronic stable and vasoplastic anginal pectoris.

The applications were submitted as simple abridged “informed consent” applications, according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to previously granted applications for Amlodipine 5mg and 10mg Tablets (PL 19156/0033 and 0034), which were originally approved in May 2007 to Jubilant Pharmaceuticals BV.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to that of previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PAR was generated for it.

The active ingredient is amlodipine besilate, a dihydropyridine calcium antagonist. 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 cardiac and vascular smooth muscle.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 29831/0451-2
PROPRIETARY NAME: Amlodipine 5mg and 10mg Tablets
ACTIVE(S): Amlodipine besilate
COMPANY NAME: Wockhardt UK Limited
LEGAL STATUS: POM

1. INTRODUCTION
These are simple, informed consent applications for Amlodipine 5mg and 10mg Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK.

The applications cross-refer to Amlodipine 5mg and 10mg Tablets (PL 19156/0033 and 0034), which were originally approved in May 2007 to Jubilant Pharmaceuticals BV.

The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The names of the products are Amlodipine 5mg and 10mg Tablets. The products have been named in-line with current requirements.

2.2 Strengths, pharmaceutical form, route of administration, container and pack sizes
The products contain amlodipine besilate, equivalent to either 5mg or 10mg amlodipine. They are stored in aluminium/polyvinylchloride blisters in pack sizes of 28 or 30 tablets. The proposed shelf-life (3 years) and storage conditions (store in the original package) are consistent with the details registered for the cross-reference products.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative compositions
The compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.
2.8 **Finished product/shelf-life specification**
The finished product specifications are in-line with the details registered for the cross-reference products.

2.9 **Drug substance specification**
The drug substance specification is consistent with the details registered for the cross-reference products.

2.10 **TSE Compliance**
Suitable statements have been provided to confirm that none of the excipients are sourced from animal/human origin. These details are consistent with those for the cross-reference products.

3. **EXPERT REPORTS**
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. **PRODUCT NAME AND APPEARANCE**
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. **SUMMARY OF PRODUCT CHARACTERISTICS**
The proposed summaries are consistent with the details registered for the cross-reference products.

6. **PATIENT INFORMATION LEAFLET/CARTON**

   **PIL**
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. The 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. 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.

   **Carton and blister**
The proposed artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. **CONCLUSIONS**
The data submitted with the applications are acceptable. The grant of marketing authorisations is recommended.
**PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to previously granted applications for Amlodipine 5mg and 10mg Tablets (PL 19156/0033 and 0034), which were originally approved in May 2007 to Jubilant Pharmaceuticals BV.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

RISK: BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with amlodipine besilate is considered to have demonstrated the therapeutic value of the compound. The risk:benefit is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 19/03/2009.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 23/03/2009.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on 02/07/2009 and 24/08/2009.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 24/07/2009 and 09/09/2009.</td>
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<td>5</td>
<td>The applications were determined on 29/09/2009</td>
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AMLODIPINE 5MG TABLETS
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STEPS TAKEN AFTER ASSESSMENT

<table>
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<th>Date submitted</th>
<th>Application type</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 5 mg amlodipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

The tablets are white, circular, biconvex and plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

4.2 Posology and method of administration
In 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.

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

Use in children and adolescents (less than 18 years of age)
Not recommended.

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

Patients with hepatic impairment
See section 4.4 "Special warnings and special precautions for use".

Patients with 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.

4.3 Contraindications
Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.
4.4 Special warnings and precautions for use

Use in patients with heart failure
In a long term, placebo controlled study, 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 impaired hepatic function
As with all calcium antagonists, amlodipine's 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.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

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 glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

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 single oral dose of amlodipine 10mg in in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: 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 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atrovastatin.

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

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. 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 cyclosporine.

Drug/Laboratory test interactions: None known.
4.6 **Pregnancy and lactation**

**Pregnancy**
Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

**Lactation**
Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

4.7 **Effects on ability to drive and use machines**
Clinical experience with amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 **Undesirable effects**
The frequencies mentioned are subdivided on categories according to following percentages:

- **Very common:** more then 10%
- **Common:** 10% or less, but more then 1%
- **Uncommon:** 1%, or less, but more then 0,1%,
- **Rare:** 0,1 % or less, but more then 0,01%
- **Very rare:** 0,01% and less (this includes isolated reports).

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

- **Blood and the lymphatic system disorders**
  - Very rare: thrombocytopenia, leucocytopenia

- **Immune system disorders**
  - Very rare: allergic reaction

- **Metabolic and nutrition disorders**
  - Very rare: hyperglycaemia

- **Psychiatric disorders**
  - Uncommon: mood changes, insomnia

- **Nervous system disorders**
  - Common: somnolence
  - Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia
  - Very rare: peripheral neuropathy

- **Eye disorders**
  - Uncommon: visual disturbances

- **Ear and Labyrinth disorders**
  - Uncommon: tinnitus

- **Cardiac disorders**
  - Common: Palpitations
  - Rare: syncope
  - Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation
Vascular disorders
Uncommon: hypotension
Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, rhinitis
Very rare: coughing

Gastrointestinal disorders
Common: Abdominal pain
Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth
Very rare: pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary disorders
Very rare: abnormal liver function tests, hepatitis, jaundice,

Skin and subcutaneous tissue disorders
Uncommon: alopecia, pruritus, perpura, skin discolouration, increased sweating
Very rare: erythema multiforme, angioedema and urticaria

Musculoskeletal, connective tissue and bone disorders
Uncommon: myalgia, arthralgia, muscle cramps and back pain

Renal and urinary disorders
Uncommon: increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders
Uncommon: impotence, gynaecomastia

General disorders and administration site conditions
Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

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 (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. 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. In healthy volunteers, the use of charcoal up to 2h 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 – Dihydropyridine derivatives.
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 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.
Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

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 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.

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) in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, 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.

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.

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

**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.

5.3 Preclinical safety data

None.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose (E460)
Sodium starch glycollate
Sodium acid citrate (E331)
Magnesium stearate (E572)
Croscarmellose sodium
Crospovidone

6.2 Incompatibilities
None stated.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
No special precautions for storage.
Store in the original packaging.

6.5 Nature and contents of container
Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0451

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/09/2009

10 DATE OF REVISION OF THE TEXT
29/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

The tablets are white, circular, biconvex and plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

4.2 Posology and method of administration
In 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.

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

Use in children and adolescents (less than 18 years of age)
Not recommended.

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

Patients with hepatic impairment
See section 4.4 "Special warnings and special precautions for use".

Patients with 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.

4.3 Contraindications
Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.
4.4 Special warnings and precautions for use

Use in patients with heart failure
In a long term, placebo controlled study, 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 impaired hepatic function
As with all calcium antagonists, amlodipine's 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.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

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 glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

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 single oral dose of amlodipine 10mg in in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: 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 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atrovastatin.

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

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. 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 cyclosporine.

Drug/Laboratory test interactions: None known.
4.6 Pregnancy and lactation

Pregnancy
Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

Lactation
Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines
Clinical experience with amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects
The frequencies mentioned are subdivided on categories according to following percentages:

- Very common: more than 10%
- Common: 10% or less, but more than 1%
- Uncommon: 1%, or less, but more than 0.1%,
- Rare: 0.1% or less, but more than 0.01%,
- Very rare: 0.01% and less (this includes isolated reports).

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

- Blood and the lymphatic system disorders
  - Very rare: thrombocytopenia, leucocytopenia

- Immune system disorders
  - Very rare: allergic reaction

- Metabolic and nutrition disorders
  - Very rare: hyperglycaemia

- Psychiatric disorders
  - Uncommon: mood changes, insomnia

- Nervous system disorders
  - Common: somnolence
  - Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia
  - Very rare: peripheral neuropathy

- Eye disorders
  - Uncommon: visual disturbances

- Ear and Labyrinth disorders
  - Uncommon: tinnitus

- Cardiac disorders
  - Common: Palpitations
  - Rare: syncope
  - Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation
Vascular disorders
Uncommon: hypotension
Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, rhinitis
Very rare: coughing

Gastrointestinal disorders
Common: Abdominal pain
Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth
Very rare: pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary disorders
Very rare: abnormal liver function tests, hepatitis, jaundice,

Skin and subcutaneous tissue disorders
Uncommon: alopecia, pruritus, perpura, skin discoloration, increased sweating
Very rare: erythema multiforme, angioedema and urticaria

Musculoskeletal, connective tissue and bone disorders
Uncommon: myalgia, arthralgia, muscle cramps and back pain

Renal and urinary disorders
Uncommon: increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders
Uncommon: impotence, gynaecomastia

General disorders and administration site conditions
Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

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 (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdose 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. In healthy volunteers, the use of charcoal up to 2h 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 – Dihydropyridine derivatives.
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 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.
Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

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 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.

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) 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 despite no significant difference in the incidence of worsening heart failure as compared to placebo.

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.

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 to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

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.

5.3 Preclinical safety data

None.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose (E460)
Sodium starch glycollate
Sodium acid citrate (E331)
Magnesium stearate (E572)
Croskarmellose sodium
Crospovidone

6.2 Incompatibilities
None stated.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
No special precautions for storage.
Store in the original packaging.

6.5 Nature and contents of container
Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Wockhardt UK Ltd
Ash Road North
Wrexham LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 29831/0452

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/09/2009

10 DATE OF REVISION OF THE TEXT
29/09/2009
MHRA PAR – Amlodipine 5mg and 10mg Tablets (PL 29831/0451-2)

PACK LEAFLET: INFORMATION FOR THE USER

Amlodipine 5 mg tablets
Amlodipine 10 mg tablets

Read all of this leaflet carefully before you start taking this medicine, including the following information about its use and possible side effects. If you have any further questions, ask your doctor or pharmacist.

1. WHAT AMLODIPINE IS AND WHAT IT IS USED FOR

Amlodipine belongs to a group of medicines called calcium antagonists. Amlodipine is used to treat:

- high blood pressure
- chest pain due to narrowing of the coronary arteries of the heart muscle (angina pectoris) or the more rare form of chest pain caused by narrowing of the coronary arteries of the heart muscle (angina vasospastic).

If you suffer from high blood pressure, Amlodipine works by relaxing blood vessels, so that blood passes through from more easily.

If you suffer from angina, Amlodipine works by relaxing blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Amlodipine does not provide immediate relief of chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE

Do not take Amlodipine:

- if you are allergic to amlodipine or similar calcium channel blockers (the usual derivatives or generic equivalents) or to any of the other ingredients (for a full list of ingredients, see section 6).

- if you have very low blood pressure.

- if you are suffering from insufficient blood supply to your tissues with symptoms like:
  - light-headedness.
  - rapid pulse.
  - a feeling of faintness or dizziness.

- if you have heart failure after a heart attack within the last four weeks.

- if you are already being treated with Verapamil (\textit{see section 4 of this leaflet}).

If you are breast-feeding, do not take Amlodipine. Please contact your doctor. Ask your doctor or pharmacist for advice before taking any medicines.

3. HOW TO TAKE AMLODIPINE

DOSAGE

Amlodipine is taken orally. Please read the instructions on the packaging of the product carefully before you start taking this medicine. Amlodipine may not be affected by your ability to drive or operate machinery. However, some patients experience side effects such as drowsiness or sleepiness, related to the fall in the blood pressure (see section 4 of this leaflet). Such side effects are more likely to occur after beginning to take Amlodipine or after dose increases. If you experience these side effects, you should refrain from driving or other activities requiring alertness.

3. HOW TO TAKE AMLODIPINE

DOSAGE

Amlodipine should be taken as instructed by your doctor. Your doctor will tell you how much you should take and when. Take it regularly, even if you feel better. If you forget to take a tablet, take it as soon as you remember, but do not take 2 tablets in one go. If you are still too high after 24 hours, consult your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amlodipine can cause side effects, although not everybody gets them. The following side effects have been observed during treatment with Amlodipine:

Blood and lymphatic system disorders

Very rare:

- reduced number of white blood cells, which may cause unexplained fever, sore throat, and flu-like symptoms (leukopenia).
- reduced number of blood (platelets in blood, which may cause easy bruising or nasal bleeding (thrombocytopenia).

Metabolism disorders

Very rare:

- increase of the blood sugar level.
- reduced levels of blood cholesterol (cholesterol dystrophy).

Nervous system disorders

Very rare:

- feeling unusual, feeling dizzy, feeling hatched, problems with sleeping, feeling tired, feeling confused, feeling worried.

Eye disorders

Very rare:

- irritability.

If you think you are taking Amlodipine tablets

Your doctor has told you that you should take Amlodipine. If you stop the treatment suddenly, your symptoms may come back. Do not stop the treatment earlier without discussing it with your doctor. Amlodipine is usually used for long term treatment.

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

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