Public Assessment Report

Mutual Recognition Procedure

Amlodipine 5mg Tablets
PL 00289/0489

Amlodipine 10mg Tablets
PL 00289/0490

UK/H/1158/001-002/MR

Teva UK Limited

LAY SUMMARY

Amlodipine 5mg and 10mg Tablets

This is a summary of the public assessment report (PAR) for Amlodipine 5mg and 10mg Tablets. It explains how Amlodipine 5mg and 10mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Amlodipine 5mg and 10mg Tablets.

For practical information about using Amlodipine 5mg and 10mg Tablets patients should read the package leaflet or contact their doctor or pharmacist.

What are Amlodipine 5mg and 10mg Tablets and what are they used for?
Amlodipine 5mg and 10mg Tablets are 'generic medicines'. This means that Amlodipine 5mg and 10mg Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Istin 5mg and 10mg Tablets (Pfizer Limited, UK).

Amlodipine 5mg and 10mg 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.

How do Amlodipine 5mg and 10mg Tablets work?
In patients with high blood pressure amlodipine work 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. Amlodipine does not provide immediate relief of chest pain from angina.

How are Amlodipine 5mg and 10mg Tablets used?
Amlodipine 5mg and 10mg Tablets should be swallowed with a glass of water. The tablets should be taken at the same time each day and can be taken before or after food and drinks. The tablets should not be taken with grapefruit juice.

The usual initial dose of amlodipine is 5 mg once daily. The dose can be increased to 10 mg once daily.

For children and adolescents (6-17 years old) the 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. The 2.5 mg dose can be obtained with Amlodipine 5 mg Tablets as these tablets can be divided into two equal doses. Amlodipine 10 mg Tablets can also be divided into equal doses.

These medicines can only be obtained with a prescription.

What benefits of Amlodipine 5mg and 10mg Tablets have been shown in studies?
Because Amlodipine 5mg and 10mg Tablets are generic medicines, studies in patients have been limited to tests to determine that Amlodipine 5mg and 10mg Tablets are bioequivalent to the reference medicines, Istin 5mg and 10mg Tablets. Two medicines are bioequivalent when they produce the same levels of active substance in the body.

What are the possible side effects of Amlodipine 5mg and 10mg Tablets?
Because Amlodipine 5mg and 10mg Tablets are generic medicines, their benefits and possible side effects are taken as being the same as those of the reference medicines.

For the full list of restrictions, see the package leaflet.

Why are Amlodipine 5mg and 10mg Tablets approved?
It was concluded that, in accordance with EU requirements, Amlodipine 5mg and 10mg Tablets have been shown to be comparable to Istin 5mg and 10mg Tablets. Therefore, the MHRA decided that, as for Istin 5mg and 10mg Tablets, the benefits of Amlodipine 5mg and 10mg Tablets are greater than their risks.

What measures are being taken to ensure the safe and effective use of Amlodipine 5mg and 10mg Tablets?
Suitable safety information has been included in the Summaries of Product Characteristics and the package leaflet for Amlodipine 5mg and 10mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Amlodipine 5mg and 10mg Tablets
The Marketing Authorisations for Amlodipine 5mg and 10mg Tablets were granted on 2 March 2007.

The full PAR for Amlodipine 5mg and 10mg Tablets follows this summary.

For more information about treatment with Amlodipine 5mg and 10mg Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2015.

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I Introduction

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Amlodipine 5mg and 10mg Tablets could be approved. These prescription only medicines (POM) are used for the treatment of hypertension, prophylaxis of chronic stable angina pectoris and Prinzmetal's (variant) angina when diagnosed by a cardiologist.

These applications were made under Article 10(1) of Directive 2001/83/EC, as amended, as so-called generic applications. The reference medicinal products for these applications are Istin Tablets 5 and 10mg (PL 00057/0297-0298), which were first authorised to Pfizer Limited on 18 September 1989. The reference products have been authorised in the EEA for at least 10 years, therefore, the legal basis of these applications is acceptable.

Following grant of the marketing authorisations in the UK, a Mutual Recognition Procedure (MRP) took place, with the UK as Reference Member State (RMS) and AT, BE, BG, CZ, DK, EE, EL, HU, IE, IT, LT, LU, LV, NL, PL, PT, SE, SI and SK as Concerned Member State (CMS). The MRP concluded on 13 May 2008.

The tablets contain the active ingredient amlodipine besilate, which is a type of medicine known as a calcium-channel blocker. It relieves heart problems by widening blood vessels to allow more blood through. This helps reduce blood pressure and relieve the strain on heart muscles.

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

Assurance has been provided that the bioequivalence study has been conducted according to the principles of Good Clinical Practice (GCP).

Acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, copies of current manufacturer authorisations issued by inspection services of the competent authorities have been provided as certification that acceptable standards of GMP are in place at those sites.

The MHRA considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder 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. The lack of a Risk Management Plan (RMP) with these applications is aceptable as the applications were submitted on 1 October 2002.

The lack of an Environmental Risk Assessment (ERA) with these applications for generic products is acceptable.

The Marketing Authorisations were granted on 2 March 2007.

II Quality aspects

II.1 Introduction

The tablets are white and round with one slightly concave side that has a breakline and is debossed and a slightly convex side that is plain. The 5mg and 10 mg tablets are 8 mm and 11 mm in diameter, respectively, and debossed with “A5”and “A10”, respectively

The tablet can be divided into equal doses.

The excipients in the medicinal products are microcrystalline cellulose, calcium hydrogen, phosphate anhydrous, sodium starch glycolate (type A) and magnesium stearate.

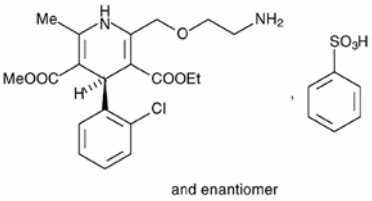
The tablets are presented in white opaque PVC/PVdC-aluminium blisters in cardboard boxes. Pack sizes of 14 (10mg tablets only), 15, 20, 28, 30, 30 (3 x 10), 50, 56, 84, 90, 98, 100, 112 and 300 (5mg tablets only) tablets have authorised, as well as calendar packs of 28 and hospital packs of 50. Not all pack sizes may be marketed.

II.2 Drug 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

Structure:



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

Molecular weight: 567.1

All aspects of the manufacture and control of the active substance, amlodipine besilate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability and the amlodipine besilate complies with current European Pharmacopoeia monograph requirements.

II.3 Medicinal Products

Pharmaceutical development

The aim of the pharmaceutical development of Amlodipine 5mg and 10mg Tablets was to develop generic versions of the innovator products, Istin Tablets 5 and 10mg.

All excipients comply with their European Pharmacopoeia monographs. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
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.

Stability of the products
Stability studies were performed in accordance with current guidelines on batches of the finished products, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 5 years for the products when the storage precautions "Do not store above 25°C", "Store in the original packaging" and "Keep the blister in the outer carton" are applied.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

II.5 SmPC, PIL and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following product labelling was approved:

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Blister:

Carton:


Amlodipine 5 mg tablets:
Each tablet contains 5 mg of amlodipine (as besilate).
DOSAGE:
Use as directed by the doctor.
Please read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
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.
Amlodipine 5 mg Tablets
Please affix dispensary label here
LOT:
EXP:
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/0489
12345-M
POM
® UK Reg'd T.M.
5 017007 023364
Amlodipine
5 mg Tablets
Oral Use
28
Calendar Pack
Tablets
5
mg
TEVA
47 x 18
x 134mm

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Blister:

Carton:

III Non-clinical aspects

III.1 Introduction

No new non-clinical data have been submitted and none are required for applications of this type. The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory.

III.2 Pharmacology

No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the formulations of Amlodipine 5mg and 10mg Tablets are intended for generic substitution, they will not lead to an increased exposure to the environment. An ERA is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV Clinical aspects

IV.1 Introduction
The applicant has submitted reports of a bioequivalence study in support of these applications. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
A comparative, randomised, three-way, three-period, single-dose crossover bioequivalence study was performed on healthy fasted volunteers, comparing the applicant's 10mg test product versus Istin 10mg Tablets (Pfizer Limited, UK) and Norvasc 10mg Tablets (Pfizer Limited, The Netherlands).

Serum drug levels were followed for 216 hours following dosing, for accurate determination of AUC_{inf} and C_{max}, followed by washout periods of 21 days between phases.

Bioequivalence results for log-transformed test/reference ratios (with 90% confidence intervals) are presented below:

AUC_t	1.01 (0.97 – 1.06)
AUC_{inf}	1.01 (0.97 – 1.06)
C_{max}	1.02 (0.98 – 1.07)
T_{max}	7 hrs (test) 8 hrs (reference)

Based on the submitted bioequivalence data, it can be considered that the applicant's Amlodipine 10mg Tablets is a generic medicinal product to Istin 10mg Tablets and Norvasc 10mg Tablets.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets.

The dissolution data and other biowaiver criteria are acceptable.

IV.3 Pharmacodynamics
No new pharmacodynamic data are required for these applications and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety
With the exception of the data generated during the bioequivalence study, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The lack of a Risk Management Plan (RMP) with these applications is aceptable as the applications were submitted on 1 October 2002.

IV.7 Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended.

The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

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 compound. The benefit/risk balance is, therefore, considered to be positive.

VII Steps taken for assessment

1	The MHRA received the marketing authorisation applications on 1 October 2002
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 13 November 2002
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 20 February 2003, and further information relating to the quality dossiers on 23 December 2003, 16 October 2006 and 18 January 2007.
4	The applicant responded to the MHRA's requests, providing further information on 13 May 2003 for the clinical sections, and again on 23 June 2004, 29 November 2006 and 13 February 2007 for the quality sections.
5	The applications were determined on 2 March 2007

VIII Steps taken after initial authorisation

Date submitted	Application type	Scope	Outcome
18/05/2007	PIU Leaflet	User Testing leaflet	Approved - 23/10/2007
23/04/2007	Outgoing MRP	Mutual Recognition applications UK/H/1158/001-002/MR	Approved - 15/05/2008
22/08/2008	Type II Variation	To update the SmPC, leaflet and labelling texts following MRP (UK/H/1158/001-002/MR).	Approved - 22/01/2009
19/12/2008	Type IB Variation	To change the name of the medicinal product in Bulgaria only.	Approved - 20/03/2009
01/11/2007	Periodic Safety Update	PSUR period covered 01/01/02 to 31/12/06 plus addendum 01/01/07 to 30/09/07	Approved - 03/11/2009
22/05/2008	Periodic Safety Update	PSUR period covered 01/01/02 to 31/12/06 plus addendum 01/01/07 to 31/03/08	Approved - 03/11/2009
13/10/2009	Type IB Variation	To change the name of the medicinal product in Hungary only.	Approved - 23/12/2009
30/11/2009	Type II Variation	To update sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.6 (Pregnancy and lactation), 4.7 (Effects on ability to drive and use machines), 4.8 (Undesirable effects), 4.9 (Overdose), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacodynamic properties) of the SmPC and consequentially the leaflet following the outcome of EU work-sharing procedure.	Approved - 07/01/2011
15/12/2011	Type IB Variation	To update sections 4.1, 4.2, 4.4 - 4.8 and 5.1- 5.3 of the SmPC to bring it in line with Article 30 of Directive	Approved - 10/05/2012

		2001/83/EC, as amended. As a consequence, the PIL has been updated.	
30/05/2011	Renewal	Renewal	Approved - 26/09/2012
07/08/2012	Type IB Variation	To change the name of the medicinal product in Poland from Amlodipine Teva to Amlodipinum 123ratio.	Approved - 31/10/2012