Public Assessment Report

Decentralised Procedure

ISTIN 5 MG ORODISPERSIBLE TABLETS
ISTIN 10 MG ORODISPERSIBLE TABLETS

(Amlodipine besilate)

Procedure No: UK/H/5123/001-2/DC

UK Licence No: PL 00057/1389-90

PFIZER LIMITED
LAY SUMMARY

On 13 December 2012, Belgium, Estonia, Luxembourg, Poland, Portugal and the UK agreed to grant Marketing Authorisations to Pfizer Limited for the medicinal products Istin 5 mg and 10 mg orodispersible tablets (PL 00057/1389-90; UK/H/5123/001-2/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 10 January 2012. These are Prescription-Only Medicines (POM).

Istin 5 mg and 10 mg orodispersible tablets contain the active amlodipine which belongs to a group of medicines called calcium antagonists.

Istin 5 mg and 10 mg orodispersible 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, this medicine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina, this medicine works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. This medicine does not provide immediate relief of chest pain from angina.

No new or unexpected safety concerns arose from these applications and it was judged that the benefits of taking Istin 5 mg and 10 mg orodispersible tablets outweigh the risks and therefore Marketing Authorisations were granted.
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# Module 1

| **Product Name** | Istin 5 mg orodispersible tablets  
Istin 10 mg orodispersible tablets |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Full dossier, Article 8.3.</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Amlodipine besilate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Orodispersible tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5 mg and 10 mg.</td>
</tr>
</tbody>
</table>
| **MA Holder** | Pfizer Limited  
Ramsgate Road  
Sandwich  
Kent CT13 9NJ |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Belgium, Estonia, Luxembourg, Poland and Portugal |
| **Procedure Number** | UK/H/5123/001-2/DC |
| **Timetable** | Day 210– 10 January 2012. |
Module 2
Summary of Product Characteristics

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.
Module 3
Patient Information Leaflet

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.
Module 4
Labelling

The following text is the approved labelling text as agreed during the decentralised procedure. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON- 5mg tablets</td>
</tr>
</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT

Istin 5 mg orodispersible tablets
Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5 mg tablet
10 tablets
20 tablets
30 tablets
60 tablets
90 tablets
100 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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
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

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00057/1389

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Istin 5 mg orodispersible tablets
MINIMUM PARTICULARS TO APPEAR ON BLISTERS
BLISTERS – 5mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Istin 5 mg orodispensible tablets
Amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON- 10mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Istin  10mg orodispersible tablets

Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 mg tablet
10 tablets
20 tablets
30 tablets
60 tablets
90 tablets
100 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral 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
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 00057/1390

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Istin 10 mg orodispersible tablets
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</strong></th>
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<td><strong>BLISTERS – 10mg tablets</strong></td>
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<table>
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<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
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<td>Istin 10mg orodispersible tablets</td>
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<td>Amlodipine</td>
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<td>Lot</td>
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<th><strong>5. OTHER</strong></th>
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Istin 5 mg and 10 mg orodispersible tablets (PL 00057/1389-90; UK/H/5123/001-2/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Belgium, Estonia, Luxembourg, Poland and Portugal as Concerned Member States (CMS). These products are prescription-only medicines (POM).

Istin 5 mg and 10 mg orodispersible tablets are indicated for hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal’s) angina.

Amlodipine first received regulatory approval on 08 March 1989 in Belgium. These are applications for a known active substance submitted according to Article 8.3 of Directive 2001/83/EC as amended, as a line-extension to the existing amlodipine tablets and capsules range (marketed as Istin™, Norvasc® or Amlor®).

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:

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).

No new non-clinical data have been submitted, which is acceptable given that the products are a line-extension of approved product licences containing a well-known active substance.

Four bioequivalence studies (single dose) were submitted to support these applications, comparing the higher strength test product Istin 10 mg orodispersible tablets (Pfizer Limited) and the reference products Istin™ 10 mg Tablets (Pfizer, Germany) and Amlor® 10 mg Capsules (Pfizer, France). The bioequivalence studies were carried out in accordance with the Declaration of Helsinki and current Good Clinical Practice (GCP) guidelines.
With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the products are a line-extension of approved product licences containing a well-known active substance.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 13 December 2012. After the subsequent national phase, the licences were granted in the UK on 10 January 2012.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Istin 5 mg orodispersible tablets  
Istin 10 mg orodispersible tablets |
| Name(s) of the active substance(s) (INN) | Amlodipine besilate |
| Pharmacotherapeutic classification (ATC code) | Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. (C08CA01). |
| Pharmaceutical form and strength(s) | 5 mg and 10 mg orodispersible tablets. |
| Reference numbers for the Mutual Recognition Procedure | UK/H/5123/001-2/DC |
| Reference Member State | United Kingdom |
| Concerned Member State | Belgium, Estonia, Luxembourg, Poland and Portugal |
| Marketing Authorisation Number(s) | PL 00057/1389-90 |
| Name and address of the authorisation holder | Pfizer Limited  
Ramsgate Road  
Sandwich  
Kent CT13 9NJ |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

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

Structure:

Molecular formula: C_{20}H_{25}ClN_{2}O_{5}, C_{6}H_{6}O_{3}S
Molecular mass: 567.1
Appearance: Amlodipine besilate is a white or almost white powder.
Solubility: Amlodipine besilate is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and 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.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients ludiflash [consisting of mannitol (E421), crospovidone, polyvinyl acetate and povidone K 30], Prosweet N&A FL PWD (consisting of dextrose and natural and artificial flavouring agents), peppermint durarome flavour (containing flavouring preparations, corn maltodextrin and sugar), sucralose, crospovidone (Type B), colloidal anhydrous silica, xylitol (E967), ferric oxide yellow (E172) and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Ludiflash, Prosweet N&A FL PWD and peppermint durarome are controlled to suitable in-house specifications and sucralose and ferric oxide yellow (E172) which is compliant with the United States Pharmacopeia (USP) and the National Formulary (NF). The
ferric oxide yellow (E172) colouring is in compliance with current EU Directives concerning the use of colouring agents. The flavourings Prosweet N&A FL PWD and peppermint durarome are also in compliance with Council Directive 88/388/EEC on flavourings for use in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, orodispersible tablets containing 5 mg or 10 mg amlodipine (as besilate). A satisfactory account of the pharmaceutical development has been provided.

Suitable pharmaceutical development data have been provided for these applications.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and has shown satisfactory results. In addition the Marketing Authorisation Holder (MAH) has committed to perform additional process validation on future commercial scale batches.

**Finished Product Specification**

The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

All strengths of the finished product are packaged in aluminium/aluminium blister strips in pack sizes of 10, 20, 30, 60, 90, 100 and 500 tablets.

It has been stated that not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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 food.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with no special storage conditions.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

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.

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.
Conclusion
There are no objections to the approval of these products from a pharmaceutical view-point.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine besilate are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

A toxicological risk assessment of the excipients in the orodispersible tablet formulation has been provided and no safety concerns have been identified.

Since Istin 5 mg and 10 mg orodispersible tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical view-point.

III.3 CLINICAL ASPECTS
The clinical pharmacology of amlodipine besilate is well known. With the exception of the bioequivalence studies, no pharmacokinetic or pharmacodynamic data were submitted for these line-extension applications and none were required for applications of this type.

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence studies:

STUDY 1 (PIVOTAL)
A randomised, 6-sequence, 3-treatment, single-dose crossover study to compare the pharmacokinetics of the test product Istin 10 mg orodispersible tablets (Pfizer Limited) versus the reference product Istin™ 10 mg Tablets (Pfizer, Germany) in healthy adult volunteers under fasted conditions.

Following a 10 hour-fast, all volunteers received a single oral dose of the reference (Treatment A) with water, or test (Treatment B) with water, or test (treatment C) without water, as a 1 x 10 mg tablet. Subjects swallowed the Istin™ 10 mg Tablets as a whole with 240mL of ambient temperature water and were instructed not to chew the medication prior to swallowing (Treatment A). For Treatment B, subjects were initially given 20mL of water to wet the mouth by swallowing the water directly. The orodispersible tablet (ODT) was then placed on the tongue for 30 seconds without crushing or breaking the tablet with the teeth. After 30 seconds, the subjects were provided 220mL water to swallow. Subjects taking Treatment C were also given 20mL of water to wet the tongue by swallowing the water directly. Then the ODT was placed on the tongue for 30 seconds (without crushing or breaking the tablet with teeth) and swallowed with no additional water. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 168 hours post dose. The washout period between treatment periods was at least 21 days.

The pharmacokinetic results for amlodipine following single-dose administration of 10 mg amlodipine orodispersible tablets with or without water and Istin™ 10 mg Tablets are presented below (log-transformed values; geometric least squares mean and 90% confidence intervals):
STUDY 2 (PIVOTAL)
A randomised, 6-sequence, 3-treatment, single-dose crossover study to compare the pharmacokinetics of the test product Istin 10 mg orodispersible tablets (Pfizer Limited) versus the reference product Amlor® 10 mg Capsules (Pfizer, France) in healthy adult volunteers under fasted conditions.

Following an overnight fast of at least 10 hours, all volunteers received a single oral dose of the reference (Treatment A) with water, or test (Treatment B) with water, or test (treatment C) without water as a 1 x 10 mg tablet. Subjects swallowed the Amlor® 10 mg Capsules as a whole with 240mL of ambient temperature water and were instructed not to chew the medication prior to swallowing (Treatment A). For Treatment B, subjects were initially given 20mL of water to wet the mouth by swallowing the water directly. The orodispersible tablet (ODT) was then placed on the tongue for 30 seconds without crushing or breaking the tablet with the teeth. After 30 seconds, the subjects were provided 220mL water to swallow. Subjects taking Treatment C were also given 20mL of water to wet the tongue by swallowing the water directly. Then the ODT was placed on the tongue for 30 seconds (without crushing or breaking the tablet with teeth) and swallowed with no additional water. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 168 hours post dose. The washout period between treatment periods was at least 21 days.

The pharmacokinetic results for amlodipine following single-dose administration of 10 mg amlodipine orodispersible tablets with or without water and Amlor® 10 mg Capsules are presented below (log-transformed values; geometric least squares mean and 90% confidence intervals):
STUDIES A0531095 and A0531096 (SUPPORTIVE STUDIES)

Studies A0531095 and A0531096 were open-label, randomized, single-dose, crossover studies to compare the test product Istin 10 mg orodispersible tablets (Pfizer Limited) and the reference products Istin™10 mg Tablets (Pfizer, Germany) and Amlor® 10 mg Capsules (Pfizer, France)

Following an overnight fast of at least 10 hours, all volunteers received a single oral dose of the test or reference product as a 1 x 10 mg tablet or capsule. For administration of the ODT, subjects were initially given 20mL of water to wet the mouth by swallowing the water directly. The ODT was then placed on the tongue for 30 seconds without crushing or breaking the tablet with the teeth. After 30 seconds, the subjects being administered the ODT with water were provided 220mL water to swallow. For administration of the Reference treatment, subjects swallowed the Istin™ tablets or the Amlor® capsules as a whole with 240mL of ambient temperature water and were instructed not to chew the medication prior to swallowing. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 168 hours post dose. The washout period between treatment periods was at least 21 days.

The pharmacokinetic results for amlodipine following single-dose administration of 10 mg amlodipine orodispersible tablets with or without water and Istin™10 mg Tablets and Amlor® 10 mg Capsules are presented below (log-transformed values; geometric least squares mean and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Parameter (Units)</th>
<th>(A) Amlor® Capsules;</th>
<th>(B) ODT with water;</th>
<th>Ratio B:A between adjusted means* (90% CI)</th>
<th>(C) ODT without water;</th>
<th>Ratio C:A between adjusted means* (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-∞) (ng·h/mL)</td>
<td>433.8 (36)</td>
<td>442.8 (27)</td>
<td>102.7</td>
<td>424.1 (29)</td>
<td>97.9</td>
</tr>
<tr>
<td>AUC(0-last) (ng·h/mL)</td>
<td>372.0 (33)</td>
<td>385.0 (25)</td>
<td>105.6</td>
<td>368.3 (28)</td>
<td>100.4</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>6.3 (24)</td>
<td>5.9 (24)</td>
<td>(90.26-98.08)</td>
<td>5.7 (24)</td>
<td>(86.32-93.71)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>6.0 (2.0-12.0)</td>
<td>6.0 (4.0-16.0)</td>
<td>-</td>
<td>8.0 (2.0-16.0)</td>
<td>-</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>53.0 (29)</td>
<td>54.5 (18)</td>
<td>-</td>
<td>55.7 (20)</td>
<td>-</td>
</tr>
</tbody>
</table>

a: Mean (CV,%) for all except: median (range) for Tmax.
b: Ln transformed geometric least square mean

Source: Study 1093 CSR Table 1

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity.
C_{max} maximum plasma concentration
T_{max} time when maximum plasma concentration is reached
t_{1/2} Half life
AUC\textsubscript{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\textsubscript{0-\infty} area under the plasma concentration-time curve from time zero to infinity
C\textsubscript{max} maximum plasma concentration
T\textsubscript{max} time when maximum plasma concentration is reached
t\textsubscript{1/2} Half life

The 90% confidence intervals for AUC and C\textsubscript{max} for test versus reference products for amlodipine besilate for the 10 mg strength are within predefined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data show that the 10 mg orodispersible tablet test product is bioequivalent to the 10 mg tablet and capsule reference products under fasting conditions.

As the 5 mg, 10 mg strengths of the product meet the criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 10 mg strength can be extrapolated to the 5 mg strength.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

**MAA Forms**
The MAA forms are satisfactory.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**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.

**Conclusion**
There are no objections to the approval of these products from a clinical view-point.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Istin 5 mg and 10 mg orodispersible 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 and none are required for applications of this type.

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

Bioequivalence has been demonstrated between the applicant’s Istin 10 mg orodispersible tablets (Pfizer Limited) and the respective reference products Istin™ 10 mg Tablets (Pfizer, Germany) and Amlor® 10 mg Capsules (Pfizer, France). As the 5 mg and 10 mg strengths of the product meets the biowaiver criteria specified in the current guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98rev 1/Corr**), the results and conclusions of the bioequivalence studies on the 10 mg strength can be extrapolated to the 5 mg strength tablet.

SAFETY
With the exception of the bioequivalence studies, 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 safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s test product and its respective reference products. Extensive clinical experience with amlodipine besilate is considered to have demonstrated the therapeutic value of the compound. 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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