Public Assessment Report

Decentralised Procedure

Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets

(bisoprolol fumarate)

UK/H/4552/001-0006/DC

UK Licence No: PL 42357/0008-0009, 0011-0013 and 0015 (previously PL 00057/1138-43)

Amneal Pharma Europe Limited
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets (PL 42357/0008-0009, 0011-0013 and 0015; UK/H/4552/001-006/DC previously PL 00057/1138-43; UK/H/4552/001-006/DC). It explains how Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated 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 Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets.

For practical information about using Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets may be referred to as Bisoprolol film-coated tablets in this report.

What are Bisoprolol film-coated tablets and what are they used for?
Bisoprolol film-coated tablets contain the active ingredient, bisoprolol fumarate. Bisoprolol is used to treat stable heart failure. Bisoprolol is given as an additional treatment to other medications for heart failure.

Bisoprolol film-coated tablets are ‘generic’ medicines. This means that Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets are similar to reference medicines already authorised in the European Union (EU) called Emconcor CHF 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets (Merck KGaA, Germany), respectively. These medicines are also similar to Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets, which are authorised in the UK to Merck Serono Limited.

How are Bisoprolol film-coated tablets used?
Bisoprolol film-coated tablets are taken by mouth. The tablets should be swallowed with with water; they should not be crushed or chewed. Bisoprolol film-coated tablets should be taken in the morning, before, with or after breakfast.

These medicines should be taken exactly as advised by the doctor.

For further information on how Bisoprolol film-coated tablets are used, please see the Summary of Product Characteristics available on the MHRA website.

Bisoprolol film-coated tablets can only be obtained on prescription.

How do Bisoprolol film-coated tablets work?
The active ingredient, bisoprolol fumarate, belongs to the group of medicinal products that are known as beta blockers.

Heart failure occurs when the heart muscle is too weak to pump blood around adequately. This results in breathlessness and heart swelling. Bisoprolol works by slowing down the heart rate and makes the heart more efficient at pumping blood around the body.

How have Bisoprolol film-coated tablets been studied.
Because Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that they are similar to the reference medicines, Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets.
Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Pfizer Limited) provided data from the published literature on bisoprolol fumarate.

**What are the benefits and risks of Bisoprolol film-coated tablets?**

Because Bisoprolol film-coated tablets are generic medicines that are bioequivalent to the reference medicines, their benefits and risks are taken as being the same as the reference medicines.

**Why are Bisoprolol film-coated tablets approved?**

It was concluded that, in accordance with EU requirements, Bisoprolol film-coated tablets have been shown to have comparable quality and to be bioequivalent to Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets. Therefore, the view was that, as for Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets, the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Bisoprolol film-coated tablets?**

Safety information has been included in the Summaries of Product Characteristics and the package leaflet for Bisoprolol film-coated tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Bisoprolol film-coated tablets.**

Marketing Authorisations (PL 00057/1138-43; UK/H/4552/001-006/DC) were first granted in the UK to Pfizer Limited on 09 November 2011.

Subsequent Changes of Ownership (CoAs) were granted for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets (PL 00057/1138-43; UK/H/4552/001-6/DC) to change the Marketing Authorisation Holder to Amneal Pharma Europe Limited (PL 42357/0008-0009 and 0011-0013 and 0015), on 04 September 2013.

The full PAR for Bisoprolol film-coated tablets follows this summary.

For more information about treatment with Bisoprolol film-coated tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2014.
# TABLE OF CONTENTS

Module 1: Information about the initial procedure  
Page 5

Module 2: Summary of Product Characteristics  
Page 6

Module 3: Patient Information Leaflet  
Page 7

Module 4: Labelling  
Page 8

Module 5: Scientific Discussion  
Page 38

   I  Introduction  
   II About the product  
   III Scientific overview and discussion  
   III 1 Quality aspects  
   III 2 Non-clinical aspects  
   III 3 Clinical aspects  
   IV Overall conclusion and benefit/risk assessment

Module 6: Steps taken after the initial procedure  
Page 48

Annex 1  
Page 49
# Module 1

## Information about the initial procedure

| **Product Name** | Bisoprolol 1.25 mg film-coated tablets  
Bisoprolol 2.5 mg film-coated tablets  
Bisoprolol 3.75 mg film-coated tablets  
Bisoprolol 5 mg film-coated tablets  
Bisoprolol 10 mg film-coated tablets |
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
</tbody>
</table>
| **Strength** | 1.25 mg  
2.5 mg  
3.75 mg  
5 mg  
10 mg |
| **MA Holder** | Pfizer Limited  
Ramsgate Road  
Sandwich  
Kent  
CT13 9NJ  
United Kingdom |
| **Reference Member State (RMS)** | United Kingdom (UK) |
| **Concerned Member States (CMS)** | Austria (AT), Belgium (BE), the Czech Republic (CZ),  
Germany (DE), Denmark (DK), Greece (EL), Spain (ES),  
Finland (FI), France (FR), Hungary (HU), Ireland (IE), Italy (IT), Luxembourg (LU), the Netherlands (NL), Norway (NO), Poland (PL), Portugal (PT), Sweden (SE), Slovenia (SI) and the Slovak Republic (SK) |
| **Procedure Number** | UK/H/4552/001/DC  
UK/H/4552/002/DC  
UK/H/4552/003/DC  
UK/H/4552/004/DC  
UK/H/4552/005/DC  
UK/H/4552/006/DC |
| **End of Procedure** | Day 210: 06 October 2011 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) 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 Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
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<tr>
<td>Bisoprolol 1.25 mg film-coated tablets</td>
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<tr>
<td>Bisoprolol fumarate</td>
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<tr>
<td><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
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<tr>
<td>Each film-coated tablet contains 1.25 mg bisoprolol fumarate equivalent to 1.06 mg bisoprolol.</td>
</tr>
<tr>
<td><strong>3. LIST OF EXCIPIENTS</strong></td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></td>
</tr>
<tr>
<td>Film-coated tablet</td>
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<tr>
<td><strong>Blistser pack:</strong></td>
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<tr>
<td>Bisoprolol 1.25 mg film-coated tablets:</td>
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<tr>
<td>1 film-coated tablet</td>
</tr>
<tr>
<td>10 film-coated tablets</td>
</tr>
<tr>
<td>20 film-coated tablets</td>
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<td><strong>Bottle pack:</strong></td>
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<td>30 film-coated tablets</td>
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<td>500 film-coated tablets</td>
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<td><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></td>
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<td>Oral use.</td>
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<td>Read the package leaflet before use.</td>
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<td><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></td>
</tr>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
<tr>
<td><strong>7. OTHER SPECIAL WARNING (S), IF NECESSARY</strong></td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td><strong>8. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
9. **SPECIAL STORAGE CONDITIONS**

Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

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**

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 42357/0008

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

-----

16. **INFORMATION IN BRAILLE**

Bisoprolol 1.25 mg film-coated tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Bisoprolol 1.25 mg film-coated tablets</td>
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<tr>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Amneal Pharma Europe Limited</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 1.25 mg film-coated tablets

Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1.25 mg bisoprolol fumarate equivalent to 1.06 mg bisoprolol.

3. LIST OF EXCIPIENTS

-------------

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
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

Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

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

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
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14. GENERAL CLASSIFICATION FOR SUPPLY

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15. INSTRUCTIONS ON USE

......

16. INFORMATION IN BRAILLE
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON**

1. **NAME OF THE MEDICINAL PRODUCT**

   Bisoprolol 10 mg film-coated tablets
   Bisoprolol fumarate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each film-coated tablet contains 10 mg bisoprolol fumarate equivalent to 8.48 mg bisoprolol.

3. **LIST OF EXCIPIENTS**

   --------

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Film-coated tablet
   *
   **Blisters**:
   - Bisoprolol 10 mg film-coated tablets:
     - 10 film-coated tablets
     - 25 film-coated tablets
     - 30 film-coated tablets
     - 50 film-coated tablets
     - 90 film-coated tablets
     - 100 film-coated tablets
   **Bottle**:
   - 30 film-coated tablets
   - 500 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Oral use.
   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**
Store below 25 °C.
Store in the original package in order to protect from light.
HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

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

Avenue Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bisoprolol 10 mg film-coated tablets
<table>
<thead>
<tr>
<th>Minimum particulars to appear on blisters</th>
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<tbody>
<tr>
<td><strong>1. Name of the medicinal product</strong></td>
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<tr>
<td>Bisoprolol 10 mg film-coated tablets</td>
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<tr>
<td>Bisoprolol fumarate</td>
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<tr>
<td><strong>2. Name of the marketing authorisation holder</strong></td>
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<td><strong>3. Expiry date</strong></td>
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<td><strong>4. Batch number</strong></td>
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<tr>
<td>Lot</td>
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<tr>
<td><strong>5. Other</strong></td>
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PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT
Bisoprolol 10 mg film-coated tablets
Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 10 mg bisoprolol fumarate equivalent to 8.48 mg bisoprolol.

3. LIST OF EXCIPIENTS
----------

4. PHARMACEUTICAL FORM AND CONTENTS
Film-coated tablet

30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use
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
Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets. Use within 6 months after first opening the HDPE bottle.
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

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Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

-----

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 2.5 mg film-coated tablets
Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg bisoprolol fumarate equivalent to 2.12 mg bisoprolol.

3. LIST OF EXCIPIENTS

---------

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Blisters pack:

Bisoprolol 2.5 mg film-coated tablets:
10 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
100 film-coated tablets

Bottle pack:

30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
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

Store below 25 °C.
Store in the original package in order to protect from light.
HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

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

Amneal Pharma Europe Limited
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Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bisoprolol 2.5 mg film-coated tablets
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS**

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<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Bisoprolol 2.5 mg film-coated tablets</td>
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<tr>
<td>Bisoprolol fumarate</td>
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<th>4. BATCH NUMBER</th>
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<td>Lot</td>
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<tr>
<th>5. OTHER</th>
</tr>
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<tr>
<td></td>
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</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 2.5 mg film-coated tablets
Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg bisoprolol fumarate equivalent to 2.12 mg bisoprolol.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
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**

Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets: Use within 6 months after first opening the HDPE bottle.

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**

Amneal Pharma Europe Limited  
70 Sir John Rogerson’s Quay  
Dublin 2  
Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 42357/0011

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

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16. **INFORMATION IN BRAILLE**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. **NAME OF THE MEDICINAL PRODUCT**
   Bisoprolol 3.75 mg film-coated tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   Each film-coated tablet contains 3.75 mg bisoprolol fumarate equivalent to 3.18 mg bisoprolol.

3. **LIST OF EXCipients**

4. **PHARMACEUTICAL FORM AND CONTENTS**
   Film-coated tablet

   **Blistier pack:**
   Bisoprolol 3.75 mg film-coated tablets:
   10 film-coated tablets
   28 film-coated tablets
   30 film-coated tablets
   56 film-coated tablets
   100 film-coated tablets

   **Bottle pack:**
   30 film-coated tablets
   500 film-coated tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   Oral use.
   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**
Store below 25 °C.
Store in the original package in order to protect from light.
HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

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

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bisoprolol 3.75 mg film-coated tablets
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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Bisoprolol 3.75 mg film-coated tablets</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>---------</td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOTTLE LABEL</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Bisoprolol 3.75 mg film-coated tablets</td>
</tr>
<tr>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td>Each film-coated tablet contains 3.75 mg bisoprolol fumarate equivalent to 3.18 mg bisoprolol.</td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>Film-coated tablet</td>
</tr>
<tr>
<td><em>30 film-coated tablets</em></td>
</tr>
<tr>
<td><em>500 film-coated tablets</em></td>
</tr>
<tr>
<td>5. METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
<tr>
<td>7. OTHER SPECIAL WARNING (S), IF NECESSARY</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>8. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
9. SPECIAL STORAGE CONDITIONS

Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets: Use within 6 months after first opening the HDPE bottle.

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

Ameal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

------

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 5 mg film-coated tablets

Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg bisoprolol fumarate equivalent to 4.24 mg bisoprolol.

3. LIST OF EXCIPIENTS

-----------

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Blistier pack:
Bisoprolol 5 mg film-coated tablets:
7 film-coated tablets
10 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
100 film-coated tablets

Bottle pack:
30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
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

Store below 25 °C
Store in the original package in order to protect from light.
HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

### 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

Ameal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

### 12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0013

### 13. BATCH NUMBER

Lot

### 14. GENERAL CLASSIFICATION FOR SUPPLY

POM

### 15. INSTRUCTIONS ON USE

-----

### 16. INFORMATION IN BRAILLE

Bisoprolol 5 mg film-coated tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Bisoprolol 5 mg film-coated tablets</td>
</tr>
<tr>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Amneal Pharma Europe Limited</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td>5. OTHER</td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOTTLE LABEL</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 5 mg film-coated tablets
Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg bisoprolol fumarate equivalent to 4.24 mg bisoprolol.

3. LIST OF EXCIPIENTS

--------------

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
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

Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets. Use within 6 months after first opening the HDPE bottle.

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

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 7.5 mg film-coated tablets

Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 7.5 mg bisoprolol fumarate equivalent to 6.36 mg bisoprolol.

3. LIST OF EXCIPIENTS

-----------

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Blister pack:
Bisoprolol 7.5 mg film-coated tablets:
10 film-coated tablets
28 film-coated tablets
30 film-coated tablets
100 film-coated tablets

Bottle pack:
30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
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

Store below 25 °C.
Store in the original package in order to protect from light.
HDPE bottle of 500 tablets
Use within 6 months after first opening the HDPE bottle.

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

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 42357/0015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

-------

16. INFORMATION IN BRAILLE

Bisoprolol 7.5 mg film-coated tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Bisoprolol 7.5 mg film-coated tablets</td>
</tr>
<tr>
<td>Bisoprolol fumarate</td>
</tr>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Amneal Pharma Europe Limited</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td>5. OTHER</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol 7.5 mg film-coated tablets

Bisoprolol fumarate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 7.5 mg bisoprolol fumarate equivalent to 6.36 mg bisoprolol.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
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

36
9. **SPECIAL STORAGE CONDITIONS**

Store below 25 °C.
Store in the original package in order to protect from light.

HDPE bottle of 500 tablets: Use within 6 months after first opening the HDPE bottle.

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

-----

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Amneal Pharma Europe Limited
70 Sir John Rogerson’s Quay
Dublin 2
Ireland

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 42357/0015

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

-----

16. **INFORMATION IN BRAILLE**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Austria, Belgium, the Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, the Slovak Republic and the UK considered that the applications for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets could be approved.

Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets are prescription only medicines (POM) and are indicated for the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

These applications for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets were submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Emconcor CHF 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets, first authorised in Sweden to Merck KGaA, Germany on 04 June 1999.

The UK reference products are Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets, first authorised to E Merck Limited on 24 December 1999 (PL 00493/0179-84 respectively). These licences then underwent a change of ownership to Merck Serono Limited on 1\textsuperscript{st} February 2010 (PL 11648/0071-3) and 2\textsuperscript{nd} February (PL 11648/0074-6).

Bisoprolol is a highly beta\textsubscript{1}-selective adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. Bisoprolol is a racemic mixture with the levorotatory form S (\texten{-}) enantiomer possessing 30 to 80 times the greater \( \beta \) blocking activity than the dextrorotatory form. Bisoprolol is absorbed and has a biological availability of about 90\% after oral administration. The kinetics of bisoprolol are linear and independent of age.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence studies, have been performed and none are required for these applications as the pharmacology of bisoprolol fumarate is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that 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.

A satisfactory justification has been provided for the absence of a Risk Management Plan.
The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 06 October 2011. After a subsequent national phase, licences were granted in the UK on 09 November 2011.

Subsequent Changes of Ownership (CoAs) were granted for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets (PL 00057/1138-43; UK/H/4552/001-6/DC) on 04 September 2013, to change the Marketing Authorisation Holder to Amneal Pharma Europe Limited (PL 42357/0008-0009 and 0011-0013 and 0015).
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Bisoprolol 1.25 mg film-coated tablets  
Bisoprolol 2.5 mg film-coated tablets  
Bisoprolol 3.75 mg film-coated tablets  
Bisoprolol 5 mg film-coated tablets  
Bisoprolol 10 mg film-coated tablets |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code) | Beta blocking agents, selective  
ATC Code: C07AB07 |
| Pharmaceutical form and strength(s)         | 1.25 mg film-coated tablets  
2.5 mg film-coated tablets  
3.75 mg film-coated tablets  
5 mg film-coated tablets  
10 mg film-coated tablets |
| Reference numbers for the Decentralised Procedure | UK/H/4552/001/DC  
UK/H/4552/002/DC  
UK/H/4552/003/DC  
UK/H/4552/004/DC  
UK/H/4552/005/DC  
UK/H/4552/006/DC |
| Reference Member State                      | United Kingdom (UK) |
| Member States concerned                     | Austria (AT), Belgium (BE), the Czech Republic (CZ), Germany (DE), Denmark (DK), Greece (EL), Spain (ES), Finland (FI), France (FR), Hungary (HU), Ireland (IE), Italy (IT), Luxembourg (LU), the Netherlands (NL), Norway (NO), Poland (PL), Portugal (PT), Sweden (SE), Slovenia (SI) and the Slovak Republic (SK) |
| Marketing Authorisation Number(s)           | PL 00057/1138  
PL 00057/1139  
PL 00057/1140  
PL 00057/1141  
PL 00057/1142  
PL 00057/1143 |
| Name and address of the authorisation holder | Pfizer Limited  
Ramsgate Road  
Sandwich  
Kent  
CT13 9NJ  
United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Active substance

INN/Ph.Eur name: Bisoprolol fumarate

Chemical name:
- (±)-1-[4-((2-(1-methyl-ethoxy)ethoxy)methyl)phenoxy]-3-((1-methylethyl)amino)-2-propanol(E)-2-butenedioate (2:1) salt.
- (±)-1-[[α-(2-isopropoxyethoxy)-p-tolyl]oxy]-3-(isopropylamino)-2-propanolfumarate(2:1) salt.

Structure:

Physical form: A white or almost white powder.
Solubility: Very soluble in water, freely soluble in methanol.

Molecular formula: C$_{40}$H$_{66}$N$_{2}$O$_{12}$
Molecular weight: 767

Bisoprolol fumarate complies with its European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability.

All potential known impurities have been identified and characterised.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference and impurity standards used. Batch analysis data are provided and comply with the proposed specification.

Stability studies have been performed with the drug substance and no significant changes of the quality parameters were observed. On the basis of the results, the RMS agreed that a suitable re-test period could be approved.
P. Medicinal Product

Other Ingredients

Other ingredients in the tablet core consist of pharmaceutical excipients microcrystalline cellulose, anhydrous calcium hydrogen phosphate, anhydrous silica colloidal, crospovidone (Type A) and magnesium stearate.

The ingredients in the tablet coating are hypromellose 6cP (E464), titanium dioxide (E171) and macrogol 400.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificate of Suitability for transmissible spongiform encephalopathies (TSE) is required.

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

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious products containing bisoprolol fumarate that could be considered generic medicinal products of Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets.

The applicant has provided suitable product development sections. Valid justifications for the use and amounts of each excipient have been provided.

Comparative in vitro assay, dissolution and impurity profiles have been provided for the proposed and reference products.

The reference products used in the bioequivalence studies are Cardicor 1.25 mg and 10 mg film-coated tablets, licensed in Germany. These products are considered to be pharmaceutically equivalent to the UK reference products.

Manufacturing Process

A satisfactory batch formula has 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. Process validation data on batches of each strength have been provided and are satisfactory.

The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification

The finished product specifications are acceptable. 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

These products are packaged in:

i) Blisters composed of cold form aluminium blisters with peelable lidding foil.

ii) High-density polyethylene (HDPE) bottles.
The pack sizes are:

**Blister packs**
- Bisoprolol 1.25 mg film-coated tablets (PL 00057/1138): 1, 10, 20, 38 and 30 film-coated tablets.
- Bisoprolol 2.5 mg film-coated tablets (PL 00057/1139): 10, 14, 28, 30 and 100 film-coated tablets.
- Bisoprolol 3.75 mg film-coated tablets (PL 00057/1140): 10, 28, 30, 56 and 100 film-coated tablets.
- Bisoprolol 5 mg film-coated tablets (PL 00057/1141): 7, 10, 28, 30, 50, 56 and 100 film-coated tablets.
- Bisoprolol 7.5 mg film-coated tablets (PL 00057/1142): 10, 28, 30 and 100 film-coated tablets.
- Bisoprolol 10 mg film-coated tablets (PL 00057/1143): 10, 28, 30, 56, 90 and 100 film-coated tablets.

**HDPE bottle packs**
All strengths: 30 and 500 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instructions ‘Store below 25°C’ and ‘Store in original package in order to protect from light’. The in-use shelf-life of the HDPE bottle 500 film-coated tablet pack size is 6 months. This is satisfactory.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling**
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved PIL and label mock-ups are included in modules 3 and 4 of this report.

User testing results of the PIL for these products have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that they contain.

**MAA forms**
The MAA forms are pharmaceutically 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**
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of bisoprolol fumarate are well-known. As bisoprolol fumarate is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory Environmental Risk Assessment (ERA) was submitted. The ERA contains a calculation of the predicted environmental concentration (PEC) in accordance with the relevant guidance (EMEA/CHMP/SWP/4447/00), using a maximum daily dose of 10 mg and default values for the other components of the equation. The calculated PEC_{surface water} exceeds the trigger value of 0.01 µg/L. The ERA concluded that for this generic product, the risk will be the same as for the originator compound. It is more appropriate to state that the use of the generic product will replace use of originator product and thus exposure of the environment to bisoprolol will not increase from use of the product.

From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS
Clinical Pharmacology

With the exception of the following bioequivalence studies, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

Bioequivalence study 1
An open-label, randomised, two-treatment, two-sequence, two-period, crossover, single-dose study to compare the pharmacokinetics of the test product Bisoprolol 1.25 mg film-coated tablets versus the reference product Cardicor (bisoprolol fumarate) 1.25 mg film-coated tablets (Merck KGaA, Germany) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 48 hours post dose. There was a washout period of 8 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for bisoprolol fumarate are presented below as log-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) (hr.pg/mL)</th>
<th>( \text{AUC}_{0-\infty} ) (hr.pg/mL)</th>
<th>( \text{C}_{\text{max}} ) (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>146727.63</td>
<td>152523.57</td>
<td>9806.53</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>156702.15</td>
<td>162814.01</td>
<td>10471.97</td>
</tr>
<tr>
<td>T/R Ratio (90% CI)</td>
<td>93.63 (90.74 – 96.62)</td>
<td>93.68 (90.63 – 96.83)</td>
<td>93.65 (89.52 – 97.96)</td>
</tr>
</tbody>
</table>

\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to \( t \) hours

\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity

\( \text{C}_{\text{max}} \) maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for \( \text{AUC}_{0-\infty} \) and \( \text{C}_{\text{max}} \) for bisoprolol fumarate lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

Bioequivalence study 2
An open-label, randomised, two-treatment, two-sequence, two-period, crossover, single-dose study to compare the pharmacokinetics of the test product Bisoprolol 10 mg film-coated tablets versus the reference product Cardicor (bisoprolol fumarate) 10 mg film-coated tablets (Merck KGaA, Germany) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 48 hours post dose. There was a washout period of 12 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for bisoprolol fumarate are presented below as log-transformed values for geometric means:
Bisoprolol fumarate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (hr.ng/mL)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (hr.ng/mL)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
</tr>
</thead>
<tbody>
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<td>Test (T)</td>
<td>602.34</td>
<td>622.35</td>
<td>40.34</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>600.97</td>
<td>621.95</td>
<td>39.21</td>
</tr>
<tr>
<td>T/R Ratio</td>
<td>100.23</td>
<td>100.07</td>
<td>102.89</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(97.38 – 103.15)</td>
<td>(97.18 – 103.04)</td>
<td>(98.66 – 107.31)</td>
</tr>
</tbody>
</table>

AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC<sub>0-t</sub> and C<sub>max</sub> for bisoprolol fumarate lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) for a biowaiver for the other strengths, the results and conclusions of the bioequivalence studies on the 1.25 mg and 10 mg strengths can be extrapolated to Bisoprolol 2.5 mg, 3.75 mg, 5 mg and 7.5 mg film-coated tablets.

Efficacy
No new efficacy data were submitted with these generic applications and none were required.

Safety
With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence studies.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PILs) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

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.

MAA Forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated 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.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Bisoprolol 1.25 mg and 10 mg film-coated tablets and the reference product Cardicor 1.25 mg and 10 mg film-coated tablets. These bioequivalence study results and conclusions can be extrapolated to Bisoprolol 2.5 mg, 3.75 mg, 5 mg and 7.5 mg film-coated tablets.

No new or unexpected safety concerns arose from the bioequivalence studies.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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 bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
The following table lists a non-safety update to the Marketing Authorisations for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets (PL 42357/0008-0009 and 0011-0013 and 0015 previously PL PL 00057/1138-43) that has been approved by the MHRA since the products were first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 December 2013</td>
<td>Type IB</td>
<td>To change the name of the medicinal product name to &quot;Stromolol&quot; in Germany, Denmark, Norway, Sweden and to &quot;Bisoprolol COR Amneal 2,5 mg / 5 mg / 10 mg comprimidos recubiertos con pelicula EFG in Spain&quot;. Also, to replace the Pfizer Summary of Pharmacovigilance system with Amneal's Summary of Pharmacovigilance system due to transfer from Pfizer (and its subsidiaries in the individual member states) to Amneal Pharma Europe Limited.</td>
<td>Approved 03 April 2014</td>
</tr>
</tbody>
</table>
Annex 1

Our Reference: PL 42357/0008, Application 0002
Product: Bisoprolol 1.25 mg tablets
Marketing Authorisation Holder: Amneal Pharma Europe Limited
Active Ingredient(s): Bisoprolol fumarate

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/4552/001/IB/003/G

Reason:
To change the name of the medicinal product name to "Stromolol" in Germany, Denmark, Norway, Sweden and to "Bisoprolol COR Amneal 2,5 mg / 5 mg / 10 mg comprimidos recubiertos con película EFG in Spain". Also, to replace the Pfizer Summary of Pharmacovigilance system with Amneal Pharma Europe Limited’s Summary of Pharmacovigilance system due to transfer from Pfizer Limited (and its subsidiaries in the individual member states) to Amneal Pharma Europe Limited.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 147409 and covers the following submissions PL 42357/0015 - 0002, PL 42357/0012 - 0002, PL 42357/0009 - 0002, PL 42357/0013 - 0002, PL 42357/0011 - 0002.

Supporting Evidence
Proposed changes to the name of the medicinal product name.
Amneal Pharma Europe Limited’s Summary of Pharmacovigilance System.

Evaluation
The submitted documentation is acceptable.

Conclusion
The proposed changes to the name of the medicinal product name in Germany, Denmark, Norway, Sweden and Spain are acceptable. No change has been made to the name of the medicinal product name in the UK.

The submitted Summary of Pharmacovigilance system is acceptable.

Decision – Approved on 03 April 2014.