Public Assessment Report

Decentralised Procedure

BREVIBLOC PREMIXED 20 MG/ML SOLUTION FOR INFUSION

(ESMOLOL HYDROCHLORIDE)

Procedure No: UK/H/2864/001/DC

UK Licence No: PL 00116/0638

BAXTER HEALTHCARE LTD
LAY SUMMARY

On 23 July 2012, Cyprus, Greece, Spain, Italy and the UK agreed to grant a Marketing Authorisation to Baxter Healthcare Ltd for the medicinal product Brevibloc Premixed 20 mg/ml Solution for Infusion (PL 00116/0638; UK/H/2864/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 04 September 2012. This product is a prescription-only medicine (POM).

Brevibloc Premixed 20 mg/ml Solution for Infusion contains a medicine called esmolol hydrochloride. It belongs to a group of medicines called ‘beta-blockers’. It works by controlling the rate and force of your heartbeat. It can also help reduce your blood pressure.

Brevibloc Premixed 20 mg/ml Solution for Infusion is used to treat:
- heartbeat problems, when your heart beats too fast
- heartbeat problems and an increase in your blood pressure if this happens during or straight after an operation

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Brevibloc Premixed 20 mg/ml Solution for Infusion outweigh the risks and a Marketing Authorisation was granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure ........................................ Page 4
Module 2: Summary of Product Characteristics ........................................... Page 5
Module 3: Patient Information Leaflet ......................................................... Page 6
Module 4: Labelling ..................................................................................... Page 7
Module 5: Scientific discussion during initial procedure ............................... Page 16
    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 Conclusions and benefit-risk assessment

Module 6  Steps taken after initial procedure ............................................. Page 24
### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Brevibloc Premixed 20 mg/ml Solution for Infusion</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10(a), well-established use</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Esmolol hydrochloride</td>
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<tr>
<td><strong>Form</strong></td>
<td>Solution for infusion</td>
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<tr>
<td><strong>Strength</strong></td>
<td>20 mg/ml</td>
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| **MA Holder** | Baxter Healthcare Ltd  
Caxton Way  
Thetford  
Norfolk,  
IP24 3SE,  
UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State (CMS)** | Cyprus, Greece, Spain and Italy |
| **Procedure Number** | UK/H/2864/001/DC |
| **Timetable** | Day 210–23 July 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

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 EU procedure number UK/H/2864/001/DC. No labelling mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-ups has been obtained.

1.3.1.2.1 Immediate Packaging

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**BAG OF 100 ml**

1. **NAME OF THE MEDICINAL PRODUCT**

   Brevibloc Premixed 20 mg/ml Solution for Infusion
   Esmolol hydrochloride

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

   Each ml contains 20 mg Esmolol hydrochloride
   Esmolol hydrochloride 2000 mg/100 ml

3. **LIST OF EXCIPIENTS**

   The other ingredients are:
   Sodium acetate
   Glacial acetic acid
   Sodium chloride
   Sodium hydroxide and/or hydrochloric acid for pH adjustment
   Water for injections
   Contains approximately 209 mg of sodium per bag. See the leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for Infusion
   1 Single Dose Bag of 100 ml

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

   For intravenous 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**

**Cautions:**
See overpouch label. Use within 24 hours of opening. Discard unused portion
Do not use the port for withdrawing an initial bolus or for adding any medications.

8. **EXPIRY DATE**

EXP MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C
Do not freeze

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

N/A

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

Baxter Healthcare Ltd
Caxton Way
Thetford
Norfolk, UK
IP24 3SE

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

PL 00116/0638

13. **BATCH NUMBER**
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<tr>
<td><strong>LOT</strong></td>
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<td><strong>14. GENERAL CLASSIFICATION FOR SUPPLY</strong></td>
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<tr>
<td>Medicinal product subject to medicinal prescription</td>
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<tr>
<td><strong>15. INSTRUCTIONS ON USE</strong></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>16. INFORMATION IN BRAILLE</strong></td>
<td>N/A</td>
</tr>
</tbody>
</table>
1.3.1.2.2 Outer Packaging: Overpouch Label

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

OVERPOUCH OF 1 BAG OF 100 ml

1. **NAME OF THE MEDICINAL PRODUCT**

   Brevibloc Premixed 20 mg/ml Solution for Infusion
   Esmolol hydrochloride

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

   Each ml contains 20 mg Esmolol hydrochloride
   Esmolol hydrochloride 2000 mg/100 ml

3. **LIST OF EXCIPIENTS**

   The other ingredients are:
   Sodium acetate
   Glacial acetic acid
   Sodium chloride
   Sodium hydroxide and/or hydrochloric acid for pH adjustment
   Water for injections
   Contains approximately 209 mg of sodium per bag. See the leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for Infusion
   Iso-Osmotic
   1 Single Dose Bag of 100 ml

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

   For intravenous 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**

**Cautions:**
After removing the overwrap, check for leaks by squeezing container firmly. If leaks are found, discard, as sterility may be impaired.
Use only if solution is clear, colourless to light yellow, and the seal is intact. Do not use if a precipitate is present.
Discard unused portion.
Do not reconnect partially used bags.
Do not remove overpouch until ready to use.
Once the seal on the port has been broken the bag should be used within 24 hours.
Do not use the port for withdrawing an initial bolus or for adding any medications.
Must not be used in series connections.

8. **EXPIRY DATE**

EXP MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C
Do not freeze

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

N/A

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

**Baxter Healthcare Ltd**
Caxton Way
Thetford
Norfolk, UK
IP24 3SE
12. MARKETING AUTHORISATION NUMBER(S)

PL 00116/0638

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medicinal prescription

15. INSTRUCTIONS ON USE

N/A

16. INFORMATION IN BRAILLE

N/A
**1.3.1.2.3 Outer Packaging: Carton Label**

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON OF 1 BAG OF 100 ml**

---

1. **NAME OF THE MEDICINAL PRODUCT**

   Brevibloc Premixed 20 mg/ml Solution for Infusion
   Esmolol hydrochloride

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

   Each ml contains 20 mg Esmolol hydrochloride
   Esmolol hydrochloride 2000 mg/100 ml

3. **LIST OF EXCIPIENTS**

   The other ingredients are:
   Sodium acetate
   Glacial acetic acid
   Sodium chloride
   Sodium hydroxide and/or hydrochloric acid for pH adjustment
   Water for injections
   Contains approximately 209 mg of sodium per bag. See the leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   Solution for Infusion
   Iso-Osmotic
   1 Single Dose Bag of 100 ml

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

   For intravenous 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**

**Cautions:**
After removing the overwrap, check for leaks by squeezing container firmly. If leaks are found, discard, as sterility may be impaired.
Use only if solution is clear, colourless to light yellow, and the seal is intact. Do not use if a precipitate is present
Discard unused portion
Do not reconnect partially used bags
Do not remove overpouch until ready to use
Once the seal on the port has been broken the bag should be used within 24 hours
Do not use the port for withdrawing an initial bolus or for adding any medications
Must not be used in series connections

8. **EXPIRY DATE**

EXP MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C
Do not freeze

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

N/A

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

**Baxter Healthcare Ltd**
Caxton Way
Thetford
Norfolk, UK
IP24 3SE
12. **MARKETING AUTHORISATION NUMBER(S)**

   PL 00116/0638

13. **BATCH NUMBER**

   LOT

14. **GENERAL CLASSIFICATION FOR SUPPLY**

   Medicinal product subject to medicinal prescription

15. **INSTRUCTIONS ON USE**

   N/A

16. **INFORMATION IN BRAILLE**

   N/A
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 application for Brevibloc Premixed 20 mg/ml Solution for Infusion (PL 00116/0638; UK/H/2864/001/DC) could be approved. This application was submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Cyprus, Greece, Spain and Italy as Concerned Member States (CMS). This product is a prescription-only medicine (POM).

Brevibloc Premixed 20 mg/ml Solution for Infusion is indicated for supraventricular tachycardia (except for pre-excitation syndromes), and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. This medicine is also indicated for tachycardia and hypertension occurring in the perioperative phase and non-compensatory sinus tachycardia where, in the physician’s judgment the rapid heart rate requires specific intervention.

This application was submitted according to Article 10(a) of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Brevibloc Premixed 20 mg/ml Solution for Infusion is a beta-selective (cardioselective) adrenergic receptor blocking agent. At therapeutic doses Brevibloc has no significant intrinsic sympathomimetic activity (ISA) or membrane stabilising activity.

Esmolol hydrochloride, the active ingredient of Brevibloc, is chemically related to the phenoxy propanolamine class of beta-blockers.

Based on the pharmacological properties Brevibloc has a rapid onset and a very short duration of action by which the dose can be quickly adjusted.

When an appropriate loading dose is used, steady state blood levels are obtained within 5 minutes. However, the therapeutic effect is achieved sooner than the stable plasma concentration. The infusion rate can then be adjusted to obtain the desired pharmacological effect.

Brevibloc has the known haemodynamic and electrophysiologic effect of beta-blockers.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

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 application could be approved with the end of procedure (Day 210) on 23 July 2012. After a subsequent national phase, the licence was granted in the UK on 04 September 2012.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Brevibloc Premixed 20 mg/ml Solution for Infusion</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Esmolol hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Beta-blocking agents, selective (C07AB09)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Solution for infusion 20 mg/ml.</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/2864/001/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State</td>
<td>Cyprus, Greece, Spain and Italy</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00116/0638</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Baxter Healthcare Ltd</td>
</tr>
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<td>Caxton Way</td>
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<td>UK</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Esmolol hydrochloride

Chemical name: \( \pm \) methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride

Structure:

\[
\begin{align*}
\text{\( \pm \)} & \text{ methyl } \text{ p-[2-hydroxy-3-(isopropylamino) propoxy]} \text{ hydrocinnamate hydrochloride} \\
\text{Structure:} & \\
\end{align*}
\]

Molecular formula: \( \text{C}_{16}\text{H}_{26}\text{NO}_{4}\text{Cl} \)
Molecular mass: 331.8

Appearance: Esmolol hydrochloride is a white to off-white, essentially odourless powder or agglomerated powder.

Solubility: Esmolol hydrochloride is freely soluble in water, methanol, glacial acetic acid, ethanol and dichloromethane, and is slightly soluble in acetone.

Esmolol hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium acetate, glacial acetic acid, sodium chloride, sodium hydroxide and/or hydrochloric acid (for pH adjustment) and water for injections.

All excipients comply with their respective European Pharmacopoeia monographs. 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 this product.

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, more concentrated 20 mg/ml infusion product based on the existing esmolol hydrochloride 10mg/ml 10ml vial aqueous solution for IV administration and the 10mg/ml solution for infusion in a 250ml infusion bag to allow delivery of the same dosage of the drug substance in a lower fluid volume in critically ill patients where fluid balance management is required.

A satisfactory account of the pharmaceutical development has been provided.

Manufacturing Process

A description and flow-chart of the manufacturing method have been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation data on commercial-scale batches has been provided.

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

The finished product is packaged in 100 ml non-latex, polyolefinic bags with a single polyvinylchloride (PVC) port and is supplied in pack sizes of one bag.

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 18 months for the unopened product with the storage conditions “Do not store above 25°C. Do not freeze”.

The opened product is physicochemically stable for 24 hours at 2 to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the
user and would normally not be longer than 24 hours at 2 to 8°C, unless opening has taken place in controlled and validated aseptic conditions.

**Bioequivalence/bioavailability**
A bioequivalence study was not necessary to support this application.

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

PIL user-testing has been accepted based on a bridging report provided by the MAH making reference to the successful user-testing of the ‘parent’ PIL for Brevibloc 10 mg/ml Solution for Infusion. The text, content and layout of the parent PIL adequately support the ‘daughter’ PIL without the need for further user-testing. The bridging is accepted.

**Marketing Authorisation Application (MAA) form**
The MAA form is satisfactory.

**Expert report**
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 this product from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**
As the pharmacodynamic, pharmacokinetic and toxicological properties of esmolol hydrochloride 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.

Since Brevibloc Premixed 20 mg/ml Solution for Infusion is a different strength of the approved product esmolol hydrochloride 10mg/ml 10ml vial aqueous solution for IV administration and the 10mg/ml solution for infusion in a 250ml infusion, it is not likely to change the total market of esmolol hydrochloride and 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 this product from a non-clinical viewpoint.

**III.3 CLINICAL ASPECTS**
The clinical pharmacology of esmolol hydrochloride is well known. No new pharmacodynamic or pharmacokinetic data are provided or required for this application.

**Efficacy**
No new efficacy data were submitted or required for this application.
Safety
No new safety data were submitted and none were required for this application. The applicant has provided an acceptable safety review from the literature. No new safety issues have been raised from this application.

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

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 this product.

Conclusion
There are no objections to the approval of this product from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Brevibloc Premixed 20 mg/ml Solution for Infusion 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 an application of this type. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

EFFICACY
No new data were submitted and none were required for this type of application.

The efficacy of the active is well described and no new studies have been conducted. The applicant has summarised the current state of knowledge in their literature review.

SAFETY
The safety profiles of esmolol hydrochloride are well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidelines.
BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Esmolol hydrochloride is a well-known active substance. Extensive clinical experience with esmolol hydrochloride is considered to have demonstrated the therapeutic value of the product. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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