Public Assessment Report

Decentralised Procedure

Montelukast 10 mg Film-coated Tablets

(montelukast sodium)

Procedure No: UK/H/5609/001/DC

UK Licence No: PL 36390/0154

Cipla (EU) Limited
LAY SUMMARY
Montelukast 10 mg Film-coated Tablets
(montelukast sodium)

This is a summary of the public assessment report (PAR) for Montelukast 10 mg Film-coated Tablets (PL 36390/0154). It explains how Montelukast 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 Montelukast 10 mg Film-coated Tablets.

For practical information about using Montelukast 10 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Montelukast 10 mg Film-coated Tablets and what are they used for?
Montelukast 10 mg Film-coated Tablets contain the active substance montelukast (as montelukast sodium). Montelukast 10 mg Film-coated Tablets are used to treat asthma by preventing asthma symptoms during the day and night.

Asthma is a long-term disease. Asthma includes:
• Difficulty breathing because of narrowed airways. This narrowing of airways worsens and improves in response to various conditions.
• Sensitive airways that react to many things, such as cigarette smoke, pollen, cold air, or exercise.
• Swelling (inflammation) in the lining of the airways.

Symptoms of asthma include: coughing, wheezing, and chest tightness.

Montelukast 10 mg Film-coated Tablets are used:
• for the treatment of patients who are not adequately controlled on their medication and need additional therapy.
• to help prevent the narrowing of airways triggered by exercise.
• in those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast 10 mg Film-coated Tablets is a generic medicine. This means that Montelukast 10 mg Film-coated Tablets are similar to a ‘reference medicine’ already authorised in the UK called Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited).

How are Montelukast 10 mg Film-coated Tablets used?
Montelukast 10 mg Film-coated Tablets are taken by mouth. The whole tablet should be taken daily with or without food.

The recommended dose in adults 15 years of age and older is 10 mg tablet once a day.

Montelukast 10 mg Film-coated Tablets can only be obtained on prescription from a doctor.

For further information on how Montelukast 10 mg Film-coated Tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How do Montelukast 10 mg Film-coated Tablets work?
Montelukast is a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in the lungs and also cause allergy symptoms. By blocking leukotrienes, Montelukast Film-coated Tablets improves asthma symptoms and help control asthma and
improve seasonal allergy symptoms (also known as hay fever or seasonal allergic rhinitis).

**How have Montelukast 10 mg Film-coated Tablets been studied?**
Because Montelukast 10 mg Film-coated Tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Montelukast 10 mg Film-coated Tablets?**
As Montelukast 10 mg Film-coated Tablets is a generic medicine of the reference medicine, Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited), its benefits and risks are taken as being the same as those for Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited).

**Why are Montelukast 10 mg Film-coated Tablets approved?**
It was concluded that, in accordance with EU requirements, Montelukast 10 mg Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited). Therefore, the view was that, as for Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited), the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Montelukast 10 mg Film-coated Tablets?**
A risk management plan has been developed to ensure that Montelukast 10 mg Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Montelukast 10 mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Montelukast 10 mg Film-coated Tablets**
Bulgaria, Croatia, Cyprus, Czech Republic, Hungary, Malta, Romania, Slovak Republic, Slovenia, Republic of Ireland and the UK agreed to grant a Marketing Authorisation for Montelukast 10 mg Film-coated Tablets on 5th December 2014. A Marketing Authorisation was granted in the UK on 15th January 2015.

The full PAR for Montelukast 10 mg Film-coated Tablets follows this summary. For more information about treatment with Montelukast 10 mg Film-coated Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Montelukast 10 mg Film-coated Tablets (PL 36390/0154; UK/H/5609/001/DC), is approvable.

The product is a prescription-only medicine (POM) indicated in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom “as-needed” short acting β-agonists provide inadequate clinical control of asthma. In those asthmatic patients in whom Montelukast is indicated in asthma, Montelukast can also provide symptomatic relief of seasonal allergic rhinitis.

Montelukast is also indicated in the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross referred to Singular 10 mg Film-coated Tablets, authorised to Merck Sharp & Dohme Limited (PL 00025/0358) on 15th January 1998.

With the UK as the Reference Member State in this Decentralised Procedure, Cipla (EU) Limited is applying for the Marketing Authorisation for Montelukast 10 mg Film-coated Tablets in Bulgaria, Croatia, Cyprus, Czech Republic, Hungary, Malta, Romania, Slovak Republic, Slovenia and Republic of Ireland.

Montelukast is a cysteinyl leukotriene antagonist. It competitively blocks the action of leukotriene D4 (and secondary ligands LTC4 and LTE4) on this receptor in the lungs and bronchial tubes. This reduces bronchoconstriction and inflammation in asthma but it has no usable effects in acute asthma attacks.

One single-dose bioequivalence study was submitted to support this application, comparing the applicant’s test product Montelukast 10 mg Film-coated tablets (Cipla Limited, India) and the reference product Singular 10 mg Film-coated tablets (Merck Sharp & Dohme Limited, UK). The bioequivalence study report provides the statement that the study was conducted in accordance with current version of the Principles of Declaration of Helsinki (Revised Seoul, October 2008) and in compliance to the current ICH, EMA and Local ethical guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

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.
All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 206 – 5th December 2014). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 36390/0154) for this product on 15th January 2015.
II QUALITY ASPECTS

II.1 Introduction
This product is a film-coated tablet and contains 10 mg montelukast, as montelukast sodium. The excipients present are lactose monohydrate, cellulose, microcrystalline (Avicel PH 102) (E-460), croscarmellose sodium (E-463), hydroxypropylcellulose (Klucel LF), magnesium stearate and Opadry yellow 04F-82591 (HPMC 2910/hypromellose 15 cP, titanium Dioxide (E171), macrogol/PEG 6000, yellow iron oxide (E172) and red iron oxide (E172)).

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of Opadry yellow 04F-82591 which complies with an in-house specification.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packaged in plain laminated 3 Ply Alu - Alu film blisters (consisting of nylon/aluminium/polyvinylchloride (PVC) and aluminium blister Foil) containing 20, 28, 30, 50, 56, 98 and 100 tablets. Blisters (unit doses) in packages of 50 and 56 tablets are also available. Not all pack sizes may be marketed.

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.

II.2 Drug Substance

INN: Montelukast Sodium
Chemical name(s): Sodium salt of 1-[[[(1R)-1-[(3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid.

\[R-(E)\]-1-[[1-3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio[methyl]cyclopropaneacetic acid, monosodium salt

Structure:

![Chemical Structure](image)

Molecular formula: \(C_{35}H_{35}Cl\text{INaO}_{3}S\)
Molecular weight: 608.18 g/mol
Appearance: White to off-white crystalline powder.
Solubility: Freely soluble in water and in methylene chloride, freely soluble to very soluble in ethanol (96%).

Montelukast sodium is the subject of an Active Substance Master File (ASMF).
Synthesis of the drug 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 Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specifications. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate robust, stable film-coated tablets containing 10 mg montelukast that could be considered as a generic medicinal product of Singulair 10 mg Film-coated Tablets (Merck Sharp & Dohme Limited).

Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 2 years with a special storage condition “Store in the original package in order to protect from light and moisture” are set. These are satisfactory.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.
III NON-CLINICAL ASPECTS

III.1 Introduction
Montelukast is a widely used, well-known active substance. The applicant has not provided additional studies and further studies are not required for this type of application. An overview based on literature review is, thus, appropriate. The non-clinical overview has been written by an appropriately qualified person. The pharmacology, pharmacokinetics and toxicology aspects of this report were considered adequate.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for a generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of montelukast sodium are well known. The applicant has not provided additional studies and further studies are not required for this type of application. An overview based on literature review is considered appropriate.

With the exception of the bioavailability studies, no new clinical data have been submitted and none are required for applications of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted a bioequivalence study under fasting conditions.

This is a randomised, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study comparing the pharmacokinetics of the test product Montelukast 10 mg Film-coated tablets (Cipla Ltd., India) with the reference product Singulair 10 mg Film-coated tablets (Merck Sharp & Dohme Limited, UK) in 51 healthy adult subjects, under fasting conditions.

Blood samples were collected at pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 24.00 and 36.00 hours post-dose. The washout period was 7 days.
Geometric Least Square Mean, Ratios and 90% Confidence Interval for montelukast sodium (n=51)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
<td>A/B</td>
</tr>
<tr>
<td>AUC_{0-t}</td>
<td>2743.784</td>
<td>2841.496</td>
<td>96.5613</td>
</tr>
<tr>
<td>C_{max}</td>
<td>421.672</td>
<td>438.307</td>
<td>96.2048</td>
</tr>
</tbody>
</table>

*Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.

The 90% confidence intervals for AUC_{0-t} and C_{max} were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Montelukast 10 mg Film-coated tablets) and the reference formulation (Singulair 10 mg Film-coated tablets) under fasting conditions.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Montelukast 10 mg Film-coated tablets.
Summary table of Safety concerns

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
</table>
| Important identified risks | - Hypersensitivity reactions including anaphylaxis  
- Erythema nodosum, erythema multiforme  
- Upper respiratory infection  
- Increased bleeding tendency  
- Use in Patients with Galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption  
- Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury) |
| Important potential risks | - Systemic eosinophilia sometimes with clinical features of vasculitis consistent with Churg-Strauss syndrome  
- Suicidal thinking and behaviour (Suicidality)  
- Depression |
| Missing information | - Data on Patients with severe hepatic impairment  
- Use of montelukast during Pregnancy  
- It is not known if montelukast is excreted in human milk  
- No specific information is available on the treatment of overdose with montelukast  
- Data demonstrating that oral corticosteroids can be reduced when montelukast is given concomitantly  
- It is not known whether montelukast is dialyzable by peritoneal- or haemodialysis. |

Summary table of risk minimisation measures

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Hypersensitivity reactions including anaphylaxis</td>
<td>The use of montelukast is contraindicated in patients with hypersensitivity to montelukast or to any of the excipients. This safety concern has been mentioned in Section 4.3 (Contraindications) and Section 4.8 (Undesirable effects) of the SPC and Section 2 (What you need to know before you take Montelukast 10 mg tablet) and Section 4 (Possible side effects) of PIL. The patient should be monitored for any signs of hypersensitivity reactions. If any hypersensitivity reactions are seen, medical attention should be sought.</td>
<td>None</td>
</tr>
<tr>
<td>Erythema nodosum, Erythema multiforme</td>
<td>This safety concern has been mentioned in Section 4.8 (Undesirable effects) of the SPC and Section 4 (Possible side effects) of PIL. The patient should be monitored for any signs of erythema nodosum and erythema multiforme such as tender red lumps under the skin on shins or severe skin reactions. If any such signs are seen, medical attention should be sought.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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</tr>
<tr>
<td>Upper respiratory infection</td>
<td>This safety concern has been mentioned in Section 4.8 (Undesirable effects) of the SPC and Section 4 (Possible side effects) of PIL. The patient should be monitored for any signs of Upper respiratory infection. Dose modification should be applied as necessary. If any such signs reactions are seen, medical attention should be sought.</td>
<td>None</td>
</tr>
<tr>
<td>Increased bleeding tendency</td>
<td>This safety concern has been mentioned in Section 4.8 (Undesirable effects) of the SPC and Section 4 (Possible side effects) of PIL. Dose modification should be applied as necessary.</td>
<td>None</td>
</tr>
<tr>
<td>Use in Patients with Galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption</td>
<td>Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. This safety concern has been mentioned in section 4.4 “Special warnings and Precautions for use” in SPC.</td>
<td>None</td>
</tr>
<tr>
<td>Hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury)</td>
<td>This safety concern has been mentioned in Section 4.8. (Undesirable effects) of the SPC and Section 4 (Possible Side effects) of PIL.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
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<tr>
<td></td>
<td>The patient should be monitored for any signs of hepatitis while on montelukast therapy. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit /risk assessment</td>
<td></td>
</tr>
</tbody>
</table>

**Important Potential Risk**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic eosinophilia sometimes with clinical features of vasculitis consistent with Churg-Strauss syndrome</td>
<td>This safety concern has been mentioned in Section 4.4. (Special warnings and precautions for use) of the SPC and Section 4 (Possible Side effects) of PIL. The frequency of occurrence of the</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Disease causing inflammation of blood vessels (Churg-Strauss syndrome) in patients on montelukast therapy is very rare. The possibility that montelukast may be associated with emergence of Churg-Strauss syndrome is uncertain. It may generally occur in patients in whom oral corticosteroid therapy for asthma has been reduced or withdrawn. Physicians should be alert to high eosinophil (type of white blood cell) counts, rash, worsening pulmonary symptoms, heart complications, and/or damage to nerves in their patients. Patients who develop these symptoms should be checked and a decision about the continuation of montelukast therapy should be made by the doctor.</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Suicidal thinking and behaviour (Suicidality)  
This safety concern has been mentioned in Section 4.8. (Undesirable effects) of the SPC and Section 4 (Possible Side effects) of PIL. Suicidality in a form of suicidal thinking and behaviour is known to be associated with use of Montelukast. The frequency of
<table>
<thead>
<tr>
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<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>occurrence of these psychiatric disorders is estimated to be very rare (&lt;1/10,000) based on adverse reactions reported in post-marketing use.</td>
<td>None</td>
</tr>
</tbody>
</table>

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

V User consultation
User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Montelukast Paediatric 5 mg chewable tablets (UK/H/5411/02/DC). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with montelukast sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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