Public Assessment Report

Decentralised Procedure

Dexamethasone 1 mg tablets
Dexamethasone 4 mg tablets

(dexamethasone)

PRODUCT LICENCE NUMBERS:
PL 12762/0617-0618

EUROPEAN PROCEDURE NUMBERS:
UK/H/6788/001-2/DC

Mercury Pharmaceuticals Limited
LAY SUMMARY

Dexamethasone 1 mg tablets
Dexamethasone 4 mg tablets
(dexamethasone)

This is a summary of the Public Assessment Report (PAR) for Dexamethasone 1 mg and 4 mg tablets. It explains how Dexamethasone 1 mg and 4 mg 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 Dexamethasone 1 mg and 4 mg tablets.

For practical information about using Dexamethasone 1 mg and 4 mg tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone 1 mg and 4 mg tablets and what are they used for?

Dexamethasone 1 mg tablets:
The application for Dexamethasone 1 mg tablets is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Fortecortin 4 mg tablets, albeit with certain differences. In this case, Dexamethasone 1 mg tablets is a change in strength from the reference product.

Dexamethasone 1 mg tablets are recommended for the treatment of rheumatic systemic diseases (rheumatic diseases which can affect internal organs e.g. systemic lupus erythematosus), severely progressive form of active rheumatic joint inflammation (rheumatoid arthritis), e.g. forms that quickly lead to joint destruction and/or when tissue outside the joints is affected, swelling of the brain caused by brain tumours, neurosurgery, bacterial inflammation of the lining of the brain (meningitis), brain abscess, severe acute asthma attack, initial treatment of extensive acute severe skin diseases, such as erythroderma, pemphigus vulgaris, acute eczema, severe infections with intoxication-like conditions (e.g. in tuberculosis, typhoid fever), only with appropriate anti-infective therapy, supportive treatment in malignant tumours, hormone replacement therapy in reduced adrenal function or failure of adrenal function (adrenogenital syndrome) in adulthood.

Dexamethasone 4 mg tablets:
The application for Dexamethasone 4 mg tablets is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised in the European Union (EU) called Fortecortin 4 mg tablets.

Dexamethasone 4 mg tablets are recommended for the treatment of rheumatic and autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, polyartheritis nodosa), diseases of respiratory tract (e.g. bronchial asthma, croup), skin (e.g. erythroderma, pemphigus vulgaris), tuberculous meningitis only in conjunction with anti-infective therapy, diseases of blood (e.g. idiopathic thrombocytopenic purpura in adults), cerebral oedema, treatment of symptomatic multiple myeloma, acute lymphoblastic leukemia, Hodgkin’s disease and non-Hodgkin’s lymphoma in combination with other medicinal products, palliative treatment of neoplastic diseases, prophylaxis and treatment of nausea and vomiting caused by chemotherapy and prevention and treatment of vomiting after operation, within antiemetic treatment.
How do Dexamethasone 1 mg and 4 mg tablets work?
Dexamethasone 1 mg and 4 mg tablets contain the active ingredient dexamethasone, which belongs to a group of medicines called corticosteroids.

Corticosteroids are hormones that are found naturally in the body that help to keep a person healthy and well. Boosting the body with extra corticosteroid, such as dexamethasone, is an effective way to treat various illnesses involving inflammation in the body. Dexamethasone lowers inflammation, which could otherwise go on making the patient’s condition worse. The patient must take this medicine regularly to get maximum benefit from it.

How are Dexamethasone 1 mg and 4 mg tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (via the mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Dexamethasone is in the form of tablets 1 mg and 4 mg. The tablet can be divided into equal halves.

Dexamethasone is given in usual doses of 0.5 to 10 mg daily, depending on the disease being treated. In more severe disease conditions doses above 10 mg per day may be required. The dose should be titrated to the individual patient response and disease severity. In order to minimise side effects, the lowest effective possible dose should be used.

Dexamethasone administration should follow instructions for dexamethasone administration when described in the Summary of Product Characteristics of the associated treatment(s). If this is not the case, local or international treatment protocols and guidelines should be followed.

Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Long term treatment
For the long-term treatment of several conditions, after initial therapy, glucocorticoid treatment should be switched from dexamethasone to prednisone/prednisolone to reduce suppression on the function of the adrenal cortex.

Use in children
If a child is taking this medicine, it is important that the doctor monitors their growth and development at frequent intervals.
The usual dose is 0.01 to 0.1 milligrams per kilogram of body weight.

This medicine can only be obtained with a prescription. The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Dexamethasone 1 mg and 4 mg tablets have been shown in studies?
Because Dexamethasone 1 mg/4 mg tablets is a hybrid/generic medicine, studies in healthy volunteers have been limited to tests to determine that it is therapeutically
equivalent/bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Dexamethasone 1 mg and 4 mg tablets**

Because Dexamethasone 1 mg/4 mg tablets is a hybrid/generic medicine and is therapeutically equivalent/bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflets or the Summaries of Product Characteristics (SmPC) available on the MHRA website.

**Why was Dexamethasone 1 mg and 4 mg tablets approved?**

It was concluded that, in accordance with EU requirements, Dexamethasone 1 mg and 4 mg tablets have been shown to be comparable/bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Dexamethasone 1 mg and 4 mg tablets?**

A Risk Management Plan (RMP) has been developed to ensure that Dexamethasone 1 mg and 4 mg tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflets, including the appropriate precautions to be followed by healthcare professionals and patients.

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

**Other information about Dexamethasone 1 mg and 4 mg tablets**

Marketing Authorisations for Dexamethasone 1 mg and 4 mg tablets were granted in the UK to the company, Formula Pharmazeutische und chemische Entwicklungs GmbH (PL 42074/0001-02) on 04 April 2019.

The Marketing Authorisations subsequently underwent a change of ownership procedure to the company, Mercury Pharmaceuticals Limited (PL 12762/0617-0618) on 08 April 2019.

The full PAR for Dexamethasone 1 mg and 4 mg tablets follows this summary.

This summary was last updated in May 2019.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications Dexamethasone 1 mg and 4 mg tablets (PL 42074/0001-02; UK/H/6788/DC) could be approved.

The products are indicated for the treatment of the following:

Dexamethasone 1 mg tablets:
Neurology
Cerebral oedema caused by brain tumours, neurosurgery, bacterial meningitis, brain abscess.

Pulmonary and respiratory diseases
Severe acute asthma attack.

Dermatology
Oral initial treatment of extensive, severe, acute skin diseases that respond to glucocorticoids, such as erythroderma, pemphigus vulgaris, acute eczema.

Autoimmune disorders/rheumatology
Oral initial treatment of autoimmune diseases, such as systemic lupus erythematosus (especially visceral forms).
Severely progressive form of active rheumatoid arthritis, e.g. rapidly destructive forms and/or with extra-articular manifestations.

Infectology
Severe infections with toxic conditions (e.g. tuberculosis, typhoid) only with concomitant anti-infective therapy.

Oncology
Palliative treatment of malignant tumours.

Endocrinology
Congenital adrenogenital syndrome in adulthood.

Dexamethasone 4 mg tablets:
Neurology
Cerebral oedema (only with symptoms of intracranial pressure evidenced by computerised tomography) caused by a brain tumour, neuro-surgical intervention, cerebral abscess.

Pulmonary and respiratory diseases
Acute asthma exacerbations when use of an oral corticosteroid (OCS) is appropriate, croup.

Dermatology
Initial treatment of extensive, severe, acute, skin diseases responding to glucocorticoids, e.g. erythroderma, pemphigus vulgaris.

Autoimmune disorders/rheumatology
Initial treatment of autoimmune disorders like systemic lupus erythematoses.
Active phases of systemic vasculitides like panarteritis nodosa (treatment duration should be limited to two weeks in cases of concomitant positive hepatitis B serology).
Severe progressive course of active rheumatoid arthritis, e.g. fast proceeding destructive forms and/or extraarticular manifestations.
Severe systemic course of juvenile idiopathic arthritis (Still's disease).

**Haematological disorder**
Idiopathic thrombocytopenic purpura in adults.

**Infectology**
Tuberculous meningitis only in conjunction with anti-infective therapy.

**Oncology**
Palliative treatment of neoplastic diseases.
Prophylaxis and treatment of emesis induced by cytostatics, emetogenic chemotherapy within antiemetic treatment.

**Various**
Prevention and treatment of postoperative vomiting, within antiemetic treatment.

The Reference Member State (RMS) for these procedures was the UK and the Concerned Member State (CMS) was Malta.

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is therefore, particularly suitable for the use in patients with cardiac failure and hypertension.

Its anti-inflammatory potency is 7 times greater than prednisolone and, like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

Dexamethasone has a biological half-life of 36 - 54 hours and therefore is suitable in conditions where continuous glucocorticoid action is required.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine (Dexamethasone 4 mg tablets) and Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product (Dexamethasone 1 mg tablets). The reference medicinal product for both applications is Fortecortin 4 mg tablets, which was first granted a product licence in the EU by Germany to Merck Serono GmbH on 19 December 2019.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being a generic/hybrid medicinal products of a reference product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic/hybrid medicinal product of a reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).
The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and is satisfactory.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 137) on 07 March 2019. After a subsequent national phase, licences were granted in the UK to the marketing authorisation holder (MAH), Formula Pharmazeutische und chemische Entwicklungs GmbH (PL 42074/0001-02) on 04 April 2019.

The Marketing Authorisations subsequently underwent a change of ownership procedure to the current MAH, Mercury Pharmaceuticals Limited (PL 12762/0617-0618) on 08 April 2019.
II QUALITY ASPECTS

II.1 Introduction
These products consist of 1 mg or 4 mg of the active substance dexamethasone per tablet.

Dexamethasone 1 mg tablets are round, biplane, white, uncoated tablets with bevel and single scoreline. Dexamethasone 1 mg with embossing ‘D | 1’. The tablet can be divided into equal doses.

Dexamethasone 4 mg tablets are round, biplane, white uncoated tablets with bevel and single scoreline. Dexamethasone 4 mg with embossing ‘D | 4’.
The tablet can be divided into equal doses.

In addition to dexamethasone, these products also contain the excipients lactose monohydrate, microcrystalline cellulose, croscarmelose sodium and magnesium stearate.

The finished products are packaged in a PVC/PVDC blister unit dose containing 10 tablets packed into a box and are available in pack sizes of 10 x 1, 20 x 1, 30 x 1, 40 x 1, 50 x 1, 60 x 1 and 100 x1 tablets. 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 ACTIVE SUBSTANCE
rINN: Dexamethasone
Chemical Name: (8S,9R,10S,11S,13S,14S,16R,17R)-9-fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one
Molecular Formula: C_{22}H_{29}FO_{5}
Chemical Structure:

Molecular Weight: 392.47
Appearance: white or almost white, crystalline powder.
Solubility: Practically insoluble in water, sparingly in anhydrous ethanol and slightly soluble in methylene chloride.

Dexamethasone is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

II.3 DRUG PRODUCTS
Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

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

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
A description and flow-chart of the manufacturing method has been provided.

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

Finished Product Specifications
The finished product specifications are satisfactory. The test methods have been described and 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
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months with the storage ’store below 25°C and in the original pack to protect from light’, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties dexamethasone are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for hybrid/generic versions of an already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety dexamethasone is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for these type of applications. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV.2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study:

STUDY
This study was a single centre, open, randomised, single dose, two-period, two-treatment, two sequence, crossover bioequivalence study comparing the applicant’s test product Dexamethasone 4 mg tablets versus the reference product, Fortecortin 4 mg tablets (Merck Serono GmbH, Germany) in subjects under fasted conditions.

Subjects were administered a single oral dose (1 x 4 mg tablet) of the test or reference product under fasting conditions. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 5 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:
Table: Bioequivalence results summary:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point Estimate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Level of Confidence</th>
<th>Intra-subject CV (%)</th>
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<tbody>
<tr>
<td>AUC(0-6)</td>
<td>1.0000</td>
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<td>C_max</td>
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</table>

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strength of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 4 mg product strength can be extrapolated to the 1 mg strength.

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

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dexamethasone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

**Dexamethasone 1 mg tablets:**

The following text is the currently approved label text. No label mock-ups have been provided for these products. In accordance with medicines legislation, these products shall not be marketed in the UK until approval of the label mock-ups has been obtained.
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Dexamethasone 1 mg tablets
Dexamethasone 4 mg tablets
dexamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg of dexamethasone
Each tablet contains 4 mg of dexamethasone

3. LIST OF EXCIPIENTS

Also contains lactose. Read the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets
10 x 1 tablets
20 x 1 tablets
50 x 1 tablets
40 x 1 tablets
50 x 1 tablets
60 x 1 tablets
100 x 1 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

Store below 25°C and in the original pack to protect from light.

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**

Mercury Pharmaceuticals Limited
Capital House, 85 King William Street, London EC4N 7BL,
United Kingdom

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

PL 12762/0617
PL 12762/0618

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Dexamethasone 1 mg tablets
Dexamethasone 4 mg tablets

17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included
<table>
<thead>
<tr>
<th>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</th>
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<tbody>
<tr>
<td>PC:</td>
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<td>SN:</td>
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<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<table>
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<td>Dexamethasone 1 mg tablets</td>
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<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER,&lt; DONATION AND PRODUCT CODES&gt;</th>
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<td>Lot:</td>
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<th>5. OTHER</th>
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Dexamethasone 4 mg tablets:
Representative copies of the labels at the time of UK licensing are provided below.
TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the product licence are recorded in the current SmPC and/or PIL available on the MHRA website.

<table>
<thead>
<tr>
<th>Application type</th>
<th>Scope</th>
<th>Product information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Outcome</th>
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