Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Levothyroxine 25, 50 and 100 micrograms/5 ml Oral Solution

(levothyroxine sodium)

Product Licence Numbers: PL 39307/0092-0094

Syri Limited

LAY SUMMARY

Levothyroxine 25, 50 and 100 micrograms/5 ml Oral Solution

(levothyroxine sodium)

This is a summary of the Public Assessment Report (PAR) for Levothyroxine 25, 50 and 100 micrograms/5 ml Oral Solution. It explains how these products 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 these products.

These products will be referred to as Levothyroxine Oral Solution in this lay summary for ease of reading.

For practical information about using Levothyroxine Oral Solution, patients should read the Patient Information Leaflets (PILs) or contact their doctor or pharmacist.

What is Levothyroxine Oral Solution and what is it used for?
These applications are for generic medicines. This means that this medicine is the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) and the United Kingdom (UK) called Eltroxin 25 mcg/5 ml, 50 mcg/5 ml, and 100 mcg/5ml Oral Solutions (Advanz Pharma).

Levothyroxine Oral Solution is used to treat hypothyroidism, a condition in which the thyroid gland is underactive and so does not make enough thyroxine for the body's needs. Levothyroxine oral solution is also used to treat thyroid cancer and diffuse non-toxic goitre or Hashimoto's thyroiditis, conditions in which the thyroid gland becomes enlarged causing a swelling in the front of the neck.

How does Levothyroxine Oral Solution work?
Levothyroxine Oral Solution contains the active ingredient levothyroxine sodium.

How is Levothyroxine Oral Solution used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth), using the syringe provided. The syringe can be used to measure the dose by drawing the liquid to the correct mark on the syringe. For example, if the dose is 50 micrograms daily then the corresponding volume would be:

For the 25 micrograms/5 ml strength – 2 x 5 ml (10 ml in total)
For the 50 micrograms/5 ml strength – 5 ml
For the 100 micrograms/5 ml strength – 2.5 ml

Patients should take Levothyroxine oral solution on an empty stomach, usually before breakfast. Use of lower strength (25 micrograms/5 ml) is recommended when a dose volume less than 2.5 ml (of higher strengths) has to be given. Use of higher strengths is recommended when a dose volume more than 20 ml (of lower strength) has to be given.

Patients should always take this medicine exactly as a doctor or pharmacist has told them. They should check with a doctor or pharmacist if they are not sure.

Patients doctor will have decided what dose they should take each day depending on their

condition. A doctor will take blood samples at regular intervals to monitor the response to treatment.

If patients are switching from the oral solution to the tablet version of levothyroxine or from the tablet version to the oral solution of levothyroxine a doctor will monitor them more closely.

Recommended dose
For hypothyroidism:
Adults and children over 12 years:
The recommended starting dose is 50 to 100 micrograms a day, increasing by 25 to 50 micrograms every 3-4 weeks, until patients are taking the right amount for their condition. The usual maintenance dose is 100 to 200 micrograms daily.

For diffuse non-toxic goitre or Hashimoto's thyroiditis the recommended dose is 50-200 micrograms per day. For the treatment of thyroid cancer the recommended dose is 150-300 micrograms per day.

Older patients (over 50 years of age):
The recommended starting dose is 12.5 micrograms a day, increasing by 12.5 micrograms every 2 weeks until the correct dose is obtained. The usual final dose is between 50 and 200 micrograms daily. This dose also applies to patients with severe hypothyroidism and to those with heart disease.

Children between 5-12years:
The dose for children depends on their age or weight.
They will be monitored to make sure they get the right dose. The dose of 5 micrograms per kg bodyweight may be used as a guide.

Children under five years:
Levothyroxine is not suitable for children under five years of age due to the amount of the ingredient propylene glycol in the medicine.

The duration of treatment is usually for life if treated for hypothyroidism, non toxic diffuse goitre or Hashimoto's thyroiditis.

Patients should use the oral syringe provided to deliver the specific dose (see instructions below). The syringe can be used to measure the dose by drawing the liquid to the correct mark on the syringe.

For further information on how Levothyroxine Oral Solution is used, refer to the PILs and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

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

What benefits of Levothyroxine Oral Solution have been shown in studies?
Because Levothyroxine Oral Solution is a generic medicine, studies in patients have been limited to tests to determine that it is 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 Levothyroxine Oral Solution?
For the full list of all side effects reported with this medicine, see Section 4 of the PILs or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Levothyroxine Oral Solution is a generic medicine and is bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicine(s).

Why was Levothyroxine Oral Solution approved?
It was concluded that, Levothyroxine Oral Solution has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicines, 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 Levothyroxine Oral Solution?
A Risk Management Plan (RMP) has been developed to ensure that Levothyroxine Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the PILs, 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 Levothyroxine Oral Solution
Marketing Authorisations for Levothyroxine Oral Solution were granted in the United Kingdom (UK) on 05 August 2021.

The full PAR for Levothyroxine Oral Solution follows this summary.

This summary was last updated in September 2021.

TABLE OF CONTENTS

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 for Levothyroxine 25, 50 and 100 micrograms/5 ml Oral Solution (PL 39307/0092-0094) could be approved.

Levothyroxine Oral Solution is indicated in adults and children 5 years of age and above for:

- hypothyroidism (congenital or acquired)
- diffuse non toxic goitre
- goitre associated with Hashimoto's thyroiditis
- suppression therapy in thyroid carcinoma

Thyroxine (T4) is a naturally occurring hormone containing iodine, produced by the thyroid gland. It is converted to its more active principle triiodothyronine (T3) in the peripheral tissues. Receptors for T3 are found on cell membranes, mitochondria and cell nuclei. Thyroid hormones are required for normal growth and development of the body, especially the nervous system. They increase the basal metabolic rate of the whole body and have stimulatory effects on the heart, skeletal muscle, liver and kidney.
The synthetic levothyroxine contained in Levothyroxine Oral Solution is identical in effect with the naturally occurring thyroxine secreted by the thyroid.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Eltroxin 25 mcg/5 ml, 50 mcg/5 ml, and 100 mcg/5ml Oral Solutions (Advanz Pharma), that have been licensed within the UK for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. 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 are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 18 April 2019 and on 01-02 July 2021 to consider quality safety and efficacy issues. Following consideration of the applicant’s responses that were submitted, the approval of the marketing authorisations was recommended.

National marketing authorisations were granted in the United Kingdom (UK) on 05 August 2021.

II QUALITY ASPECTS

II.1 Introduction

These products consist of clear, colourless oral solution. Each 5 ml of oral solution contains 25, 50 or 100micrograms of levothyroxine sodium as an active substance.

In addition to levothyroxine sodium these products also contain the excipients propylene glycol (E1520), sodium hydroxide (E524), sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), maltitol liquid (E965), citric acid monohydrate (E330) and purified water.

The finished products are packaged in type III amber glass bottle with tamper evident, child resistant white plastic cap and polypropylene inner, polyethylene outer and expanded polyethylene (EPE) liner closure. The bottle is placed in a carton with a 5ml oral syringe with 0.1ml graduation mark and an adaptor for the syringe. The pack size is 100 ml.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

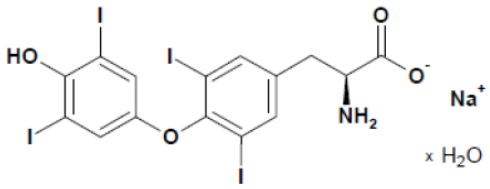
II.2 ACTIVE SUBSTANCE

rINN: Levothyroxine sodium

Chemical Name: Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl)propanoate

Molecular Formula: $C_{15}H_{10}I_4NNaO_4$ (anhydrous)

Chemical Structure:



Molecular Weight: 798.85 g/mol (anhydrous)

Appearance: Almost white or slightly brownish-yellow, fine slightly hygroscopic, crystalline powder.

Solubility: Very slightly soluble in water, slightly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides.

Levothyroxine sodium 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.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

No excipients of animal or human origin are used in the final product.

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

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

Satisfactory batch formulation data have 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.

Finished Product Specification
The finished product specifications at release and shelf-life 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 15 months, with a special storage condition ‘Do not store above 25°C’ is approved. The container should be kept in the outer carton in order to protect from light.

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 of levothyroxine sodium 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 generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation 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 of levothyroxine sodium is well known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this 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.

An open label, randomised, balanced, two treatment, two period, two sequence, single dose, truncated, crossover bioequivalence study of Levothyroxine Sodium 100 micrograms/ 5 ml oral solution with Eltroxin (Levothyroxine Sodium) 100micrograms/ 5 ml oral solution (Mercury Pharmaceuticals Ltd) in healthy, adult, human subjects under fasting conditions.

Subjects were administered a single dose of the test or the reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 42 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Primary Analysis

Geometric means, ratios and 90% confidence Intervals for Levothyroxine – Baseline corrected

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-72}	2340.9836	2463.0704	95.0433	89.4849	100.9470
C_{max}	65.5740	65.7714	99.6999	94.7095	104.9534

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

Secondary Analysis

Geometric means, ratios and 90% confidence Intervals for Levothyroxine – Baseline uncorrected

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-72}	7023.1811	7081.2279	99.1803	96.8559	101.5604
C_{max}	130.6810	130.1004	100.4463	97.6746	103.2967

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

As the additional strengths (25 and 50 mcg/5ml) of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength (100 mcg/5ml) can be extrapolated to the other strengths(25 and 50 mcg/5ml).

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 and reference products.

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 an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, 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

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Metformin hydrochloride 500 mg/5 ml oral solution (Syri Limited). The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

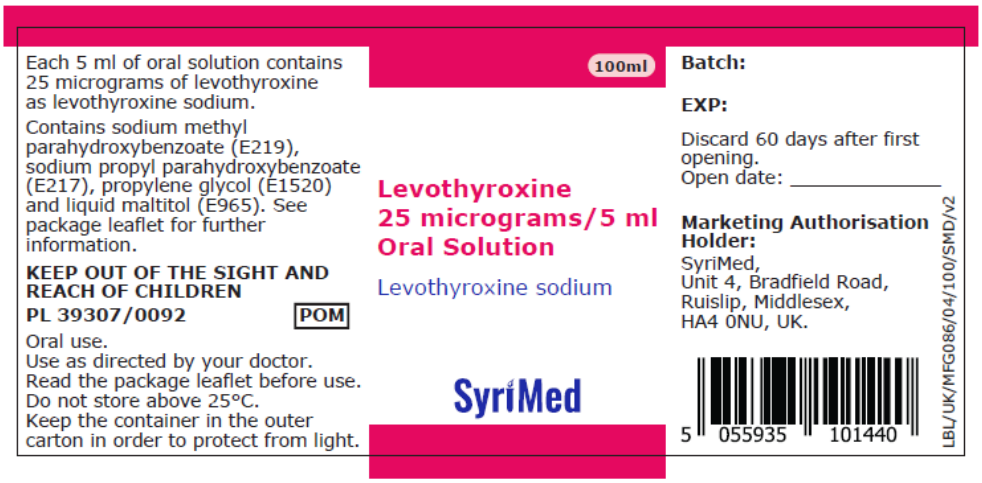
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levothyroxine sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore,

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.

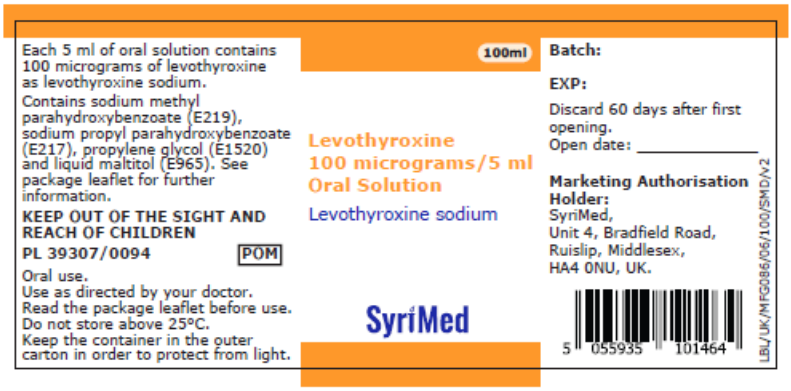
In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.




Each 5 ml of oral solution contains 50 micrograms of levothyroxine as levothyroxine sodium.
Contains sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), propylene glycol (E1520) and liquid maltitol (E965). See package leaflet for further information.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
PL 39307/0093
POM
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 25°C.
Keep the container in the outer carton in order to protect from light.
100ml
Levothyroxine 50 micrograms/5 ml Oral Solution
Levothyroxine sodium
SyriMed
Batch:
EXP:
Discard 60 days after first opening.
Open date: _____
Marketing Authorisation Holder:
SyriMed,
Unit 4, Bradfield Road,
Ruislip, Middlesex,
HA4 0NU, UK.
5 055935 101457
LBL/UK/MFG086/05/100/SMD/v2


Levothyroxine 50 micrograms/5 ml Oral Solution
Levothyroxine sodium
Affix dispensing label here
5 055935 101457
100ml
Levothyroxine 50 micrograms/5 ml Oral Solution
Levothyroxine sodium
For children aged 5 years and above and adults.
Each 5 ml of oral solution contains 50 micrograms of levothyroxine as levothyroxine sodium.
Contains sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), propylene glycol (E1520) and liquid maltitol (E965). See package leaflet for further information.
SyriMed
CRT/UK/MFG086/05/100/SMD/v2
Levothyroxine 50 micrograms/5 ml Oral Solution
Levothyroxine sodium
5+ Years
SyriMed
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
PL 39307/0093
POM
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 25°C.
Keep the container in the outer carton in order to protect from light.
Discard 60 days after first opening.
Open date: _____
This pack also contains 5 ml oral syringe and syringe adaptor.
Marketing Authorisation Holder:
SyriMed,
Unit 4, Bradfield Road,
Ruislip, Middlesex,
HA4 0NU, UK.
SyriMed


Each 5 ml of oral solution contains 100 micrograms of levothyroxine as levothyroxine sodium.
Contains sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), propylene glycol (E1520) and liquid maltitol (E965). See package leaflet for further information.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
PL 39307/0094
POM
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 25ºC.
Keep the container in the outer carton in order to protect from light.
100ml
Levothyroxine
100 micrograms/5 ml
Oral Solution
Levothyroxine sodium
SyriMed
Batch:
EXP:
Discard 60 days after first opening.
Open date: _____
Marketing Authorisation Holder:
SyriMed,
Unit 4, Bradfield Road,
Ruislip, Middlesex,
HA4 0NU, UK.
5 055935 101464
LBL/UK/MFG086/06/100/SMD/v2


Levothyroxine
100 micrograms/5 ml
Oral Solution
Levothyroxine sodium
Affix dispensing label here
5 055935 101464
100ml
Levothyroxine
100 micrograms/5 ml
Oral Solution
Levothyroxine sodium
For children aged 5 years and above and adults.
Each 5 ml of oral solution contains 100 micrograms of levothyroxine as levothyroxine sodium.
Contains sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), propylene glycol (E1520) and liquid maltitol (E965). See package leaflet for further information.
SyriMed
Levothyroxine
100 micrograms/5 ml
Oral Solution
Levothyroxine sodium
5+ Years
SyriMed
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
PL 39307/0094
POM
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 25ºC.
Keep the container in the outer carton in order to protect from light.
Discard 60 days after first opening.
Open date: _____
This pack also contains 5 ml oral syringe and syringe adaptor.
Marketing Authorisation Holder:
SyriMed,
Unit 4, Bradfield Road,
Ruislip, Middlesex,
HA4 0NU,UK.
SyriMed
CRT/UK/MFG086/06/100/SMD/v2

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 marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**