Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

HYOSCINE BUTYLBROMIDE 10 MG FILM-COATED TABLETS

HYOSCINE BUTYLBROMIDE 20 MG FILM-COATED TABLETS

hyoscine butylbromide

PL 20117/0346 and 0349 - 0350

Morningside Healthcare Ltd

LAY SUMMARY

Hyoscine Butylbromide 10 mg Film-coated Tablets
Hyoscine Butylbromide 20 mg Film-coated Tablets
hyoscine butylbromide

This is a summary of the Public Assessment Report (PAR) for Hyoscine Butylbromide 10 mg and 20 mg Film-coated Tablets. 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 Hyoscine Butylbromide Film-coated Tablets in this lay summary for ease of reading.

For practical information about using Hyoscine Butylbromide Film-coated Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Hyoscine Butylbromide Film-coated Tablets and what are they used for?
The application for Hyoscine Butylbromide 10 mg Film-coated 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 United Kingdom (UK) called Buscopan Tablets/Cramps.

The applications for Hyoscine Butylbromide 20 mg Film-coated Tablets are for hybrid medicines. This means that the medicine is similar to the reference medicine, Buscopan Tablets/Cramps, already authorised in the UK, albeit with certain differences. In this case, Hyoscine Butylbromide 20 mg Film-coated Tablets are a high strength (of the active substance) to the reference product.

Hyoscine Butylbromide Tablets are used to relieve cramps in the muscles of the
- stomach
- gut (intestine)
- bladder and the tubes that lead to the outside of the body (urinary system).

Hyoscine Butylbromide Tablets can also be used to relieve the symptoms of Irritable Bowel Syndrome (IBS).

How do Hyoscine Butylbromide Film-coated Tablets work?
Hyoscine Butylbromide Tablets contain a medicine called hyoscine butylbromide. This belongs to a group of medicines called “antispasmodics”.

How are Hyoscine Butylbromide Film-coated Tablets used?
The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (taken by mouth).

Taking these medicines
- The patient should take their tablets with water.
- The patient should not break, crush or chew the tablets.
- Hyoscine Butylbromide Tablets should not be taken continuously for long periods of time.

How much to take
Adults and children over 12 years
- The recommended dose is two tablets of 10 mg or one tablet of 20 mg, 4 times a day.
- For Irritable Bowel Syndrome, the patient's doctor may give the patient a lower starting dose of one tablet of 10 mg 3 times a day. This dose may be increased, if further relief is necessary.

Children 6 - 12 years:
- The recommended dose is one tablet of 10 mg, 3 times a day.

Hyoscine Butylbromide Tablets are not recommended for children under 6 years.

For further information on how Hyoscine Butylbromide Film-coated Tablets are used, refer to the PILs and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines 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 Hyoscine Butylbromide Film-coated Tablets have been shown in studies?
As Hyoscine Butylbromide Film-coated Tablets are generic/hybrid medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent/therapeutically equivalent 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 Hyoscine Butylbromide Film-coated Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL 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.

As Hyoscine Butylbromide Film-coated Tablets are generic/hybrid medicine and are bioequivalent/therapeutically equivalent to the reference medicine, their possible side effects are considered to be the same as the reference medicine.

Why were Hyoscine Butylbromide Film-coated Tablets approved?
It was concluded that, Hyoscine Butylbromide Film-coated Tablets have been shown to be comparable to and to be bioequivalent/therapeutically equivalent 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 Hyoscine Butylbromide Film-coated Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Hyoscine Butylbromide Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, 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 Hyoscine Butylbromide Film-coated Tablets
Marketing Authorisations for Hyoscine Butylbromide Film-coated Tablets were granted in the UK on 24 November 2021.

The full PAR for Hyoscine Butylbromide Film-coated Tablets follows this summary.

This summary was last updated in January 2022.

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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 for Hyoscine Butylbromide 10 mg and 20 mg Film-coated Tablets (PL 20117/0346 and 0349 - 0350) could be approved.

The products are approved for the following indications:

- the relief of spasm of the genito-urinary tract or gastro-intestinal tract and for the symptomatic relief of Irritable Bowel Syndrome.

Hyoscine butylbromide, the active substance, exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary and genito-urinary tracts. As a quaternary ammonium derivative, hyoscine butylbromide does not enter the central nervous system. Therefore, anticholinergic side effects at the central nervous system do not occur. Peripheral anticholinergic action results from a ganglion-blocking action within the visceral wall as well as from an anti-muscarinic activity.

The application for Hyoscine Butylbromide 10 mg Film-coated Tablets was approved under Regulation 51B of The Human Medicines Regulations 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Buscopan Tablets/Cramps (PL 00015/0047R), that has been licensed within the United Kingdom (UK) for a suitable time, in line with the legal requirements.

The applications for Hyoscine Butylbromide 20 mg Film-coated Tablets were approved under Regulation 52B of The Human Medicines Regulations 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Buscopan Tablets/Cramps (PL 00015/0047R).

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

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications are for hybrid/generic medicinal products of a suitable reference product. The bioequivalence studies were 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 23-24 January 2020 and 02-03 September 2021 because major objections were raised with respect to quality and clinical aspects of the dossier. The Committee provisionally concluded that further information on quality and clinical aspects should be requested before the products could be approved. In response to the CHM advice, the applicant provided additional data, to address the points that had been raised. Following consideration of the responses and further data that were submitted, the approval of the Marketing Authorisations was recommended.

National Marketing Authorisations were granted in the on 24 November 2021.

II QUALITY ASPECTS

II.1 Introduction

These products contain 10 mg or 20 mg of hyoscine butylbromide in each film-coated tablet.

In addition to hyoscine butylbromide, these products also contain the excipients lactose monohydrate; cellulose, microcrystalline; povidone K-30 and magnesium stearate in the tablet core. The film-coating contains polyvinyl alcohol (E1203); titanium dioxide (E171); talc (E553b); polyethylene glycol (E1521) and lecithin (E422).

The finished products are packaged in polyvinylchloride/polyvinylidene chloride-aluminium blisters, in pack sizes of 28, 56, 100 and 500 film-coated 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 regulations concerning materials in contact with food.

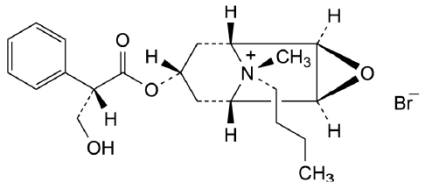
II.2 ACTIVE SUBSTANCE

rINN: Hyoscine butylbromide

Chemical Name: (1*R*,2*R*,4*S*,5*S*,7*s*,9*r*)-9-Butyl-7-[[(2S)-3-hydroxy-2-phenylpropanoyl]oxy]-9-methyl-3-oxa-9-zatricyclo[3.3.1.$0^{2,4}$]nonan-9-ium bromide

Molecular Formula: $C_{21}H_{30}BrNO_4$

Chemical Structure:



Molecular Weight: 440.4 g/mol

Appearance: White or almost white, crystalline powder

Solubility: Freely soluble in water and in methylene chloride, sparingly soluble in anhydrous ethanol

Hyoscine butylbromide 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.

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 formulation data 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 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 3 years, with no special storage conditions, 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 of hyoscine butylbromide 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

An Environmental Risk Assessment (ERA), with Phase I and persistent, bioaccumulative, toxic (PBT) risk assessment, has been provided. This is acceptable.

The derived value for Predicted Environmental Concentration$_{Surfacewater}$ ($PEC_{Surfacewater}$) for hyoscine butylbromide is 0.0004 µg/L, which is below the action point of 0.01 µg/L (the threshold for further Phase II evaluation).

The results of the ERA indicate that there is no risk of increased environmental exposure with the use of these 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 hyoscine butylbromide are well-known. With the exception of data from three bioequivalence studies, no new clinical data are provided or are required for applications of this type. An overview based on a literature review and a review of these studies is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following bioequivalence studies.

Bioequivalence study 1 (Replicate, fasting)

This study was an open-label, randomised, single dose, two-treatment, two-sequence, four-period, full replicate, crossover oral bioequivalence study comparing the test product Hyoscine Butylbromide 20 mg Film-coated Tablets versus the Polish reference product, Buscopan Forte 20 mg Tabletki Powlekane (English translation: Buscopan Forte 20 mg Film-coated Tablets), in healthy adult human subjects under fasting conditions.

Subjects received each of the test and reference treatments twice, in accordance with the sequence to which they had been randomised. In each of the four periods, after an overnight fast of at least 10 hours, a single oral dose (20 mg; 1 tablet) of either the test or the reference product was administered with approximately 240 mL of water.

Blood samples were taken pre-dose and up to 48 hours post dose. The treatment days were separated by a washout period of nine days between treatment periods 1 and 2, 10 days between treatment periods 2 and 3 and seven days between treatment periods 3 and 4.

A summary of the pharmacokinetic results is presented below:

Table 1: Geometric least squares means, ratios and 90% confidence intervals for pharmacokinetic parameters (C_{max} and AUC_{0-t}) of hyoscine butylbromide

PK parameters (units)	Geometric least squares means and ratios			Intra-subject CV of Reference Formulation (%)	Acceptance range 90% confidence intervals (%)	Calculated 90% confidence intervals (%)
	Test product (T)	Reference product (R)	T/R (%)			
C_{max} (pg/mL)	174.117	182.426	95.45	33.99	77.78-128.57	88.04-103.47
AUC_{0-t} (hr*pg/mL	1547.398	1575.058	98.24	28.13	80.00-125.00	91.76-105.18

C_{max} Maximum plasma concentration.
CV Coefficient of variation
AUC_{0-t} Area under the plasma concentration verses time curve from 0 hour to the last measurable concentration

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the Polish reference product, under fasting conditions.

Since adequate bridging has been demonstrated between the Polish and UK Buscopan reference products, the study is acceptable and a bioequivalence study undertaken against the UK reference product is not required.

Bioequivalence study 2 (single-dose, fasting conditions)
This study was an open-label, randomised, single-dose, two-treatment, two-sequence, four period, full replicate, crossover bioequivalence study comparing the test product Hyoscine Butylbromide 10 mg Tablets versus the reference Canadian product Buscopan 10 mg Tablets in healthy, adult, human subjects under fasting conditions.

Subjects received each of the test and reference treatments twice, in accordance with the sequence to which they had been randomised. In each of the 4 periods, after an overnight fast of at least 10 hours, a single oral dose (20 mg; 2 x tablets) of either the test or the reference product was administered with approximately 240 mL of water.

Blood samples were taken pre-dose and up to 48 hours post dose in each study period, with a washout period of seven days between treatment periods 1 and 2, nine days between treatment periods 2 and 3 and eight days between treatment periods 3 and 4. The total duration of the study was of 28 days from the day of admission in first period until the end of the fourth period.

A summary of the pharmacokinetic results is presented below:

Table 2: Geometric least squares means, ratios and 90% confidence intervals for pharmacokinetic parameters (C_{max} and AUC_{0-t}) of hyoscine butylbromide

PK parameters (units)	Geometric least squares means and ratios			Intra-subject CV of Reference Formulation (%)	Acceptance range 90% confidence intervals (%)	Calculated 90% confidence intervals (%)
	Test product (T)	Reference product (R)	T/R (%)			
C_{max} (pg/mL)	162.465	155.034	104.79	38.58	75.35-132.72	95.62-114.85
AUC_{0-t} (hr*pg/mL	1297.760	1179.169	110.06	29.17	80.00-125.00	102.05-118.69

C_{max} Maximum plasma concentration.
CV Coefficient of variation
AUC_{0-t} Area under the plasma concentration verses time curve from 0 hour to the last measurable concentration

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the Canadian reference product, under fasting conditions.

Since adequate bridging has been demonstrated between the Canadian and UK reference Buscupan products, the study is acceptable.

A fasting bioequivalence study alone is insufficient for locally acting products, such as hyoscine butylbromide, for which the new formulation may have differential activity on the target in the presence/absence of food in the gut lumen. In line with current guidelines, to ensure equivalence irrespective of food intake, a bioequivalence study in the fed state is also required. In response to major objections raised the applicant provided the below bioequivalence study conducted under fed conditions.

Bioequivalence study 3 (single-dose, fed conditions)
This study was an open-label, randomised, single-dose, two-treatment, two-sequence, four-period, full replicate, crossover bioequivalence study comparing the test product Hyoscine Butylbromide 20 mg Tablets (1 x 20 mg) versus the UK reference product Buscopan 10 mg Tablets (2 x10 mg) in healthy, adult, human subjects under fed conditions.

After an overnight fast, subjects were administered a single dose (20 mg) of either the test (1 x 20 mg tablet) or reference product (2 x10 mg tablets), according to randomisation, with 240 ml of water under fed conditions (30 minutes after the intake of a standard high-fat high-calorie breakfast; approximately 800 to 1000 kcal).

Blood samples were taken pre-dose and up 48 hours post dose in each study period, with a washout period of eight days between treatment periods 1 and 2, seven days between periods 2 and 3 and 11 days between treatment periods 3 and 4. Total duration of the study was thirty 30 days from the day of admission in first period until the end of the study.

A summary of the pharmacokinetic results is presented below:

Table 3 Geometric least squares means, ratios and 90% confidence intervals for pharmacokinetic parameters (C_{max} and AUC_{0-t}) of hyoscine butylbromide

PK parameters (units)	Geometric least squares means and ratios			Intra-subject CV of Reference Formulation (%)	Acceptance range 90% confidence intervals (%)	Calculated 90% confidence intervals (%)
	Test product (T)	Reference product (R)	T/R (%)			
C_{max} (pg/mL)	38.380	39.682	96.72	25.59	80.00-125.00	90.95-102.85
AUC_{0-t} (hr*pg/mL	354.136	352.862	100.36	18.43	80.00-125.00	95.03-105.99

C_{max} Maximum plasma concentration.
CV Coefficient of variation
AUC_{0-t} Area under the plasma concentration verses time curve from 0 hour to the last measurable concentration

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product (1 x 20 mg) and the reference product (2 x 10 mg) under fed conditions.

Overall conclusion of the studies
Bioequivalence between the test and reference products has been demonstrated in the fasted and fed states.

The Polish, Canadian and UK reference products all fall under the same global marketing Authorisation, and, based on quality data, adequate bridging has been demonstrated between the UK reference product and the Polish and Canadian products. Therefore, bioequivalence between the test and UK reference products has been demonstrated in the fasted and fed states.

As the 10 mg and 20 mg strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence studies on the 10 mg and 20 mg strength product strengths can be extrapolated to the respective other 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 studies, no new safety data were submitted with these applications.

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

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulations 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 study in accordance with legal requirements. The results show that the PIL 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

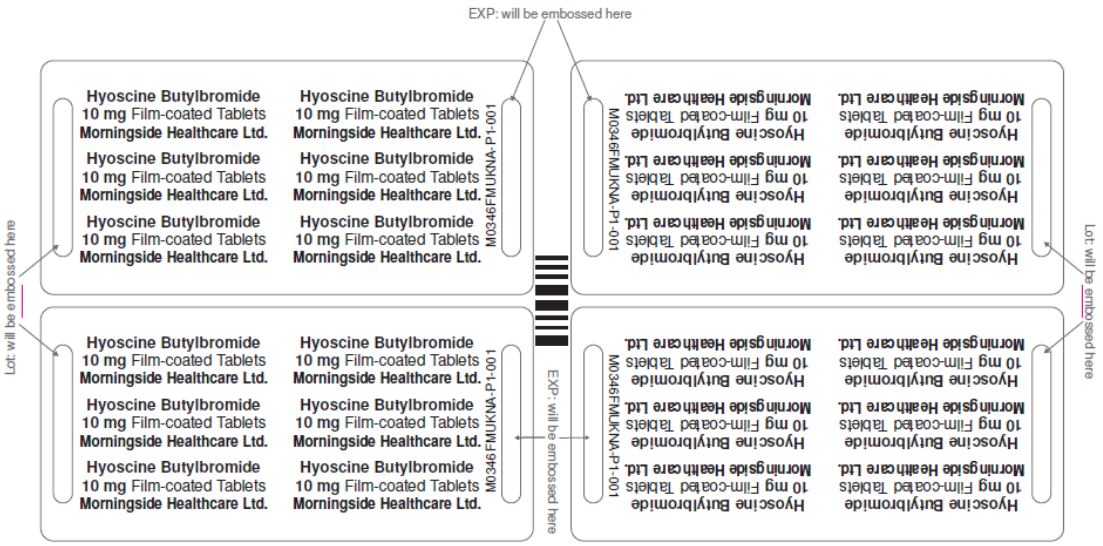
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with hyoscine butylbromide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

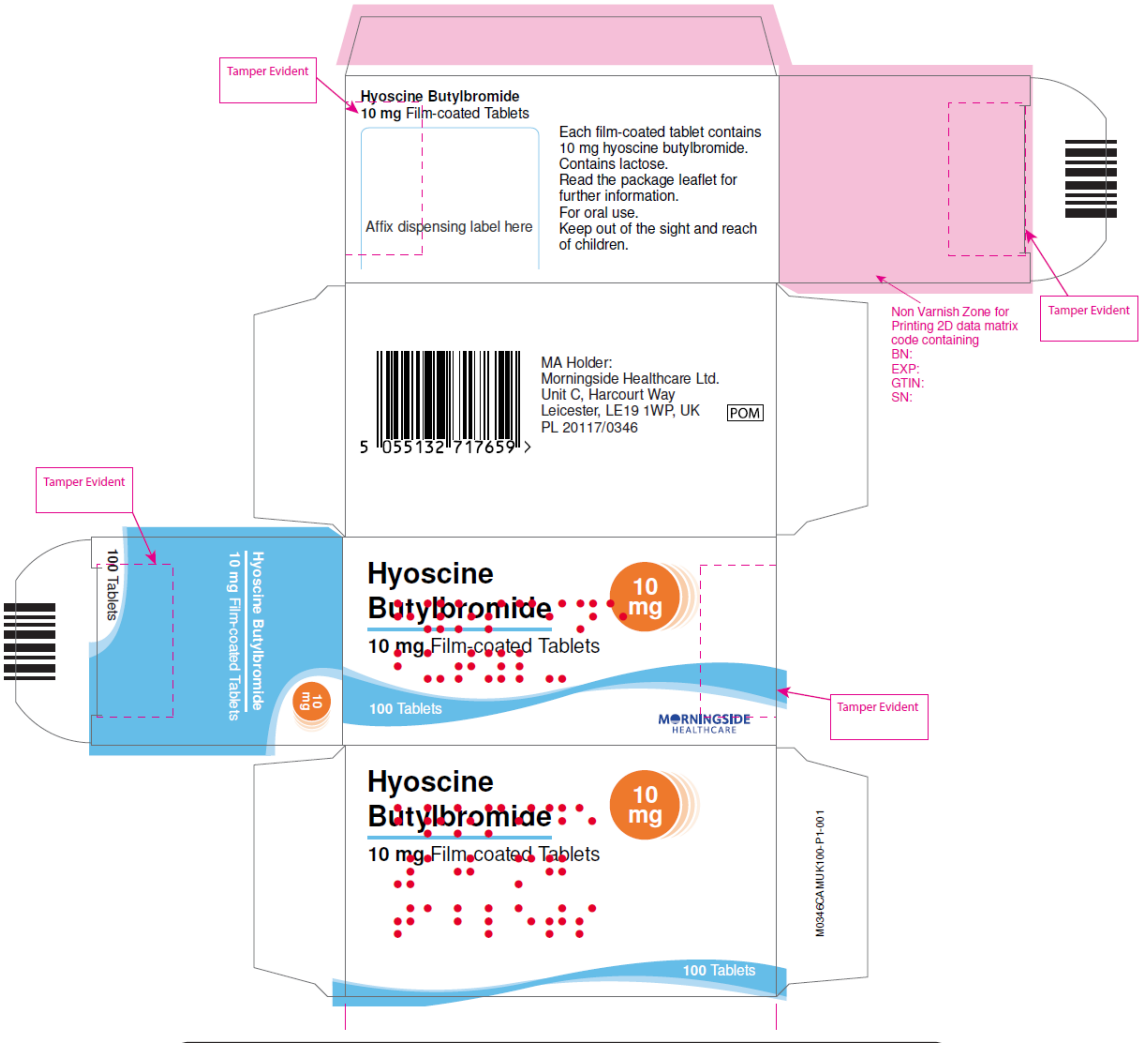
The Summaries of Product Characteristics (SmPCs), PILs and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

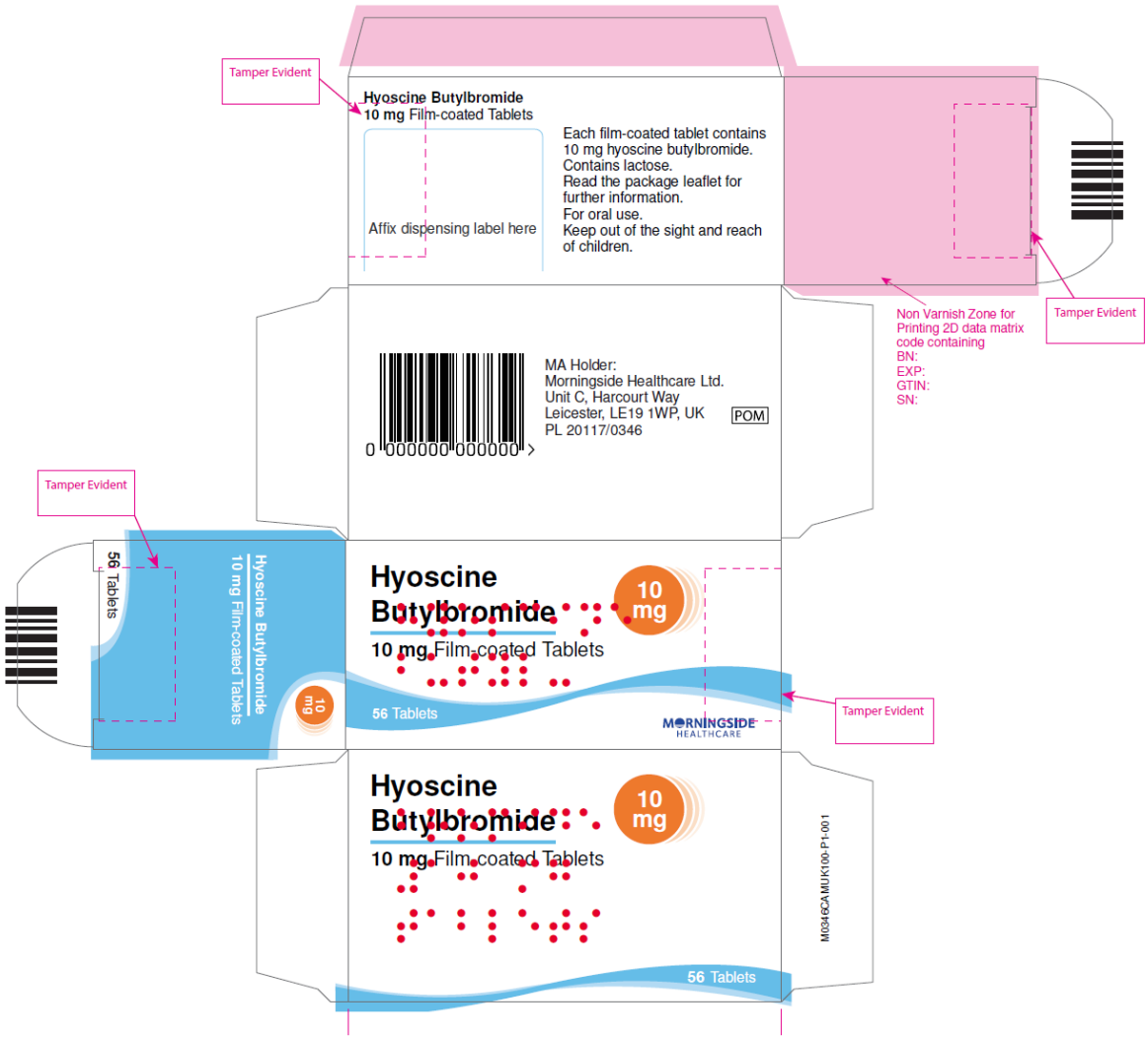
In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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

Hyoscine Butylbromide 10 mg Film-coated Tablets (PL 20117/0346)






Tamper Evident
Hyoscine Butylbromide
10 mg Film-coated Tablets
Affix dispensing label here
Each film-coated tablet contains 10 mg hyoscine butylbromide.
Contains lactose.
Read the package leaflet for further information.
For oral use.
Keep out of the sight and reach of children.
Non Varnish Zone for Printing 2D data matrix code containing
BN:
EXP:
GTIN:
SN:
Tamper Evident
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
PL 20117/0346
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Tamper Evident
56 Tablets
Hyoscine Butylbromide
10 mg Film-coated Tablets
10 mg
Hyoscine Butylbromide
10 mg
10 mg Film-coated Tablets
56 Tablets
MORNINGSIDE HEALTHCARE
Tamper Evident
Hyoscine Butylbromide
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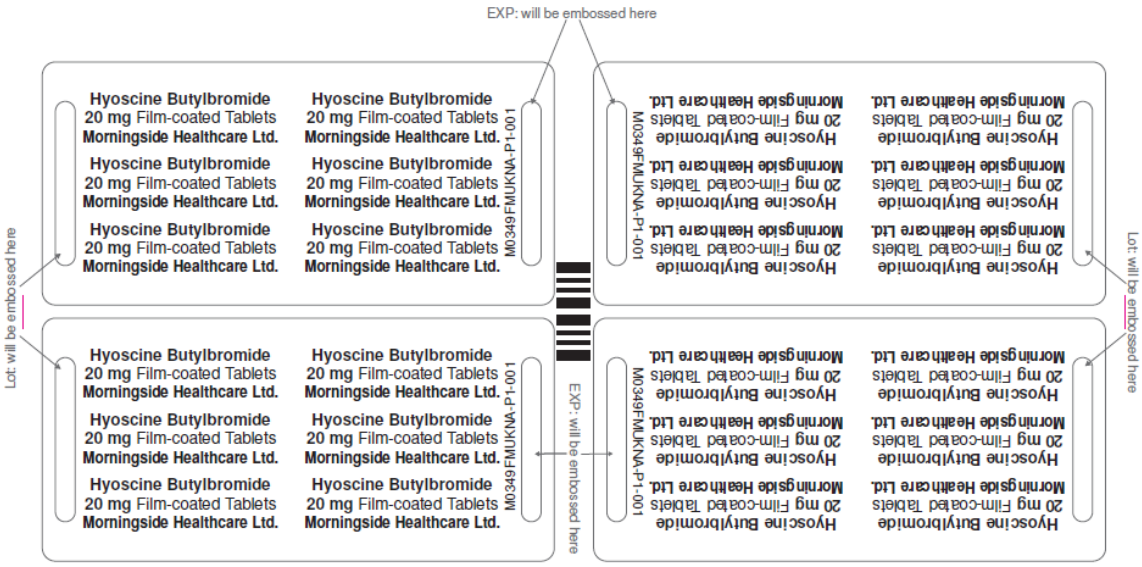
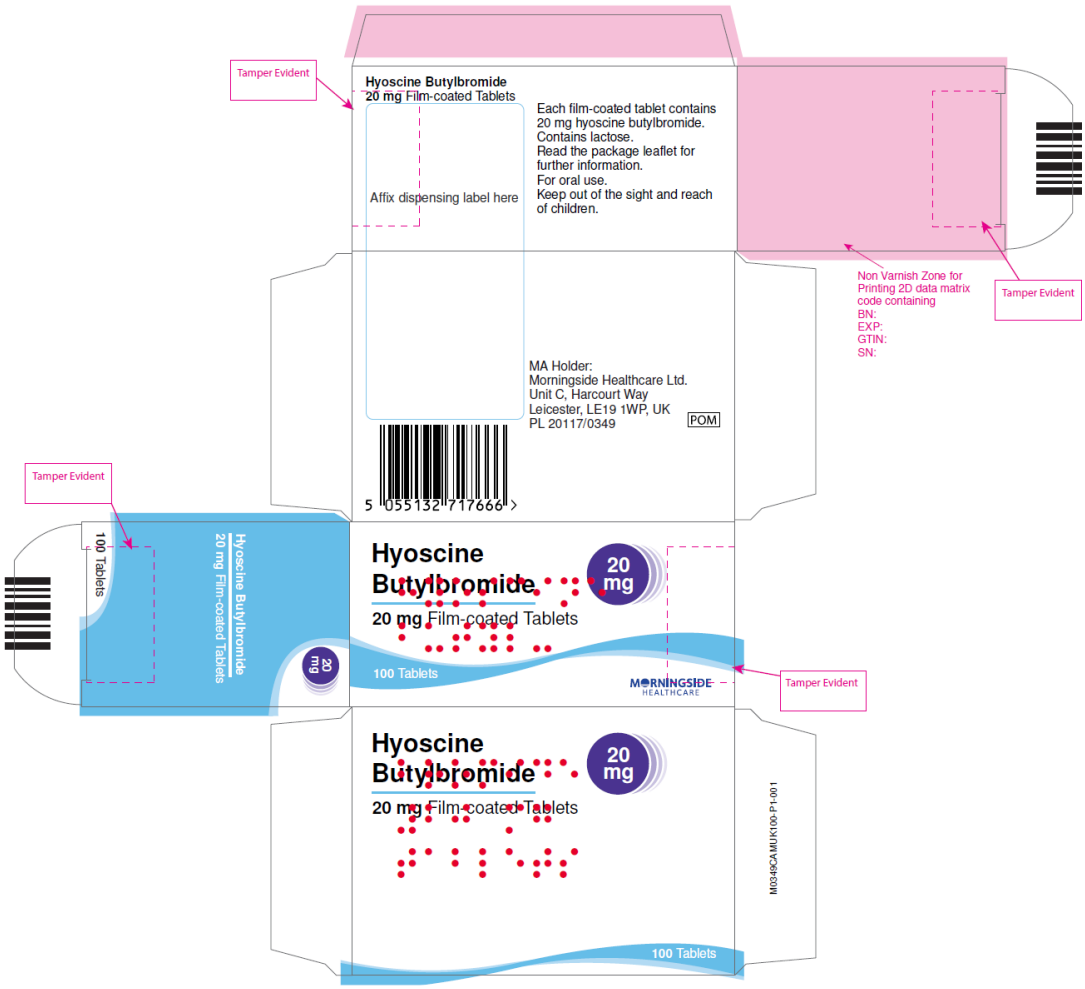
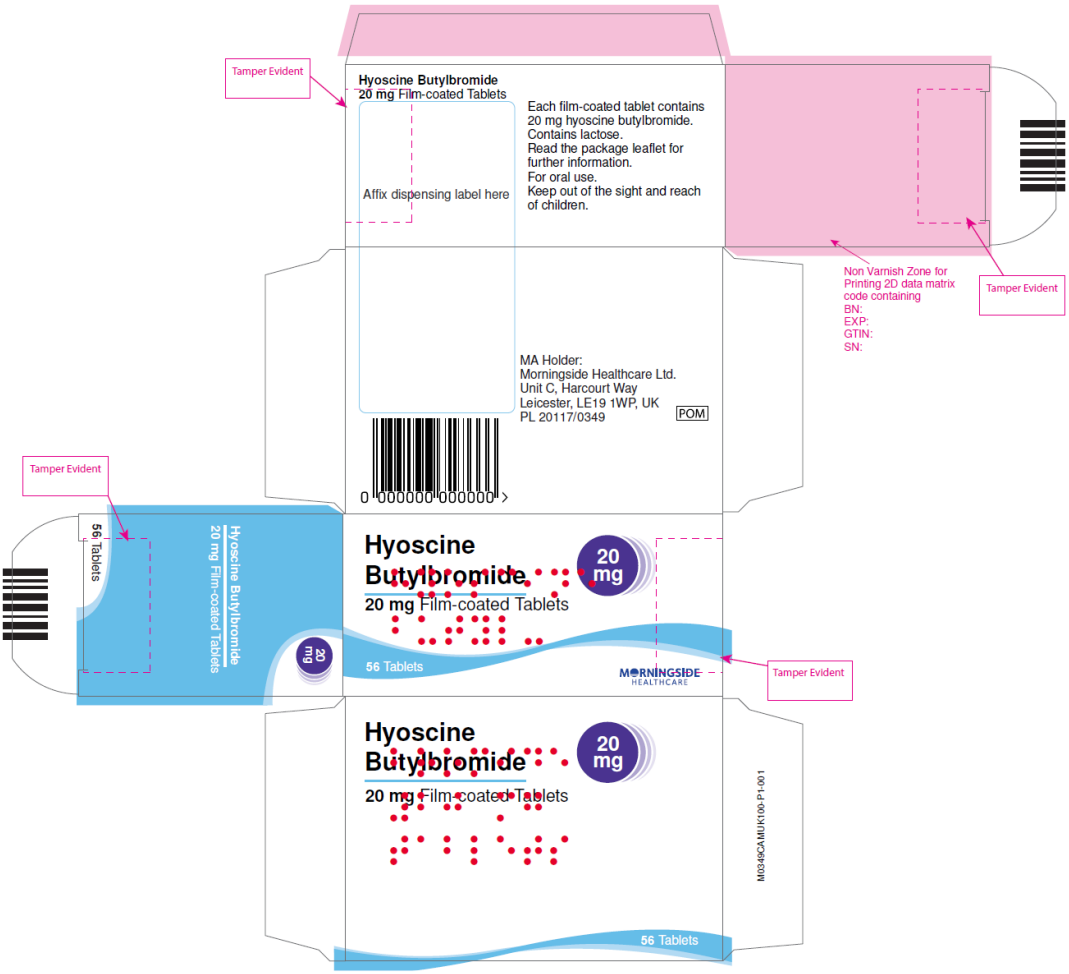
M0346CAMUK100-P1-001

Hyoscine Butylbromide 20 mg Film-coated Tablets (PL 20117/0349)






Tamper Evident
Hyoscine Butylbromide
20 mg Film-coated Tablets
Affix dispensing label here
Each film-coated tablet contains 20 mg hyoscine butylbromide.
Contains lactose.
Read the package leaflet for further information.
For oral use.
Keep out of the sight and reach of children.
Non Varnish Zone for Printing 2D data matrix code containing
BN:
EXP:
GTIN:
SN:
Tamper Evident
MA Holder:
Morningside Healthcare Ltd.
Unit C, Harcourt Way
Leicester, LE19 1WP, UK
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56 Tablets
Hyoscine Butylbromide
20 mg Film-coated Tablets
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Hyoscine Butylbromide
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Tamper Evident
Hyoscine Butylbromide
20 mg Film-coated Tablets
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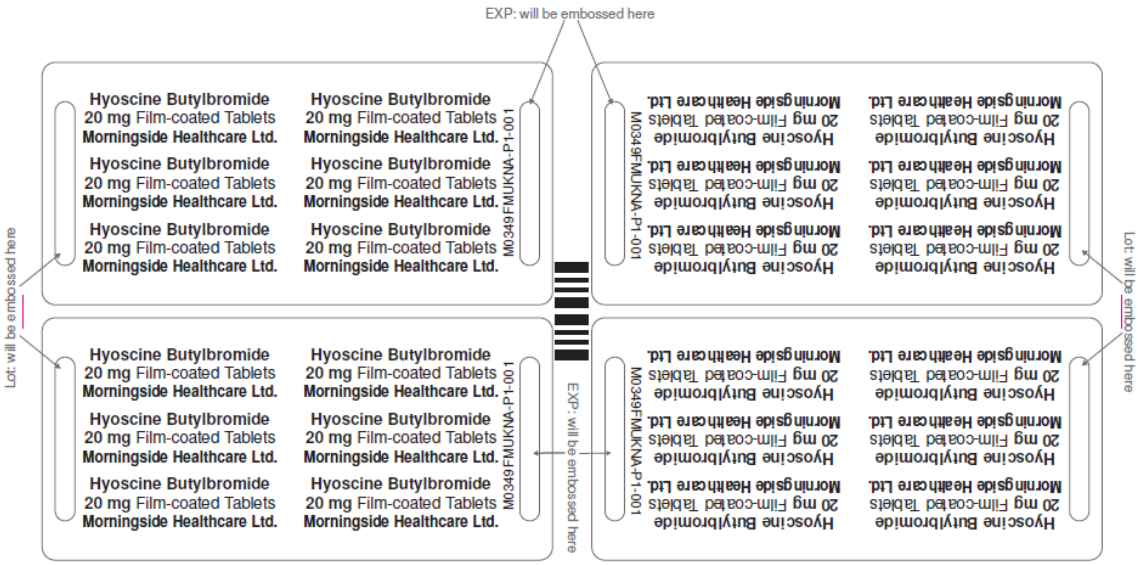
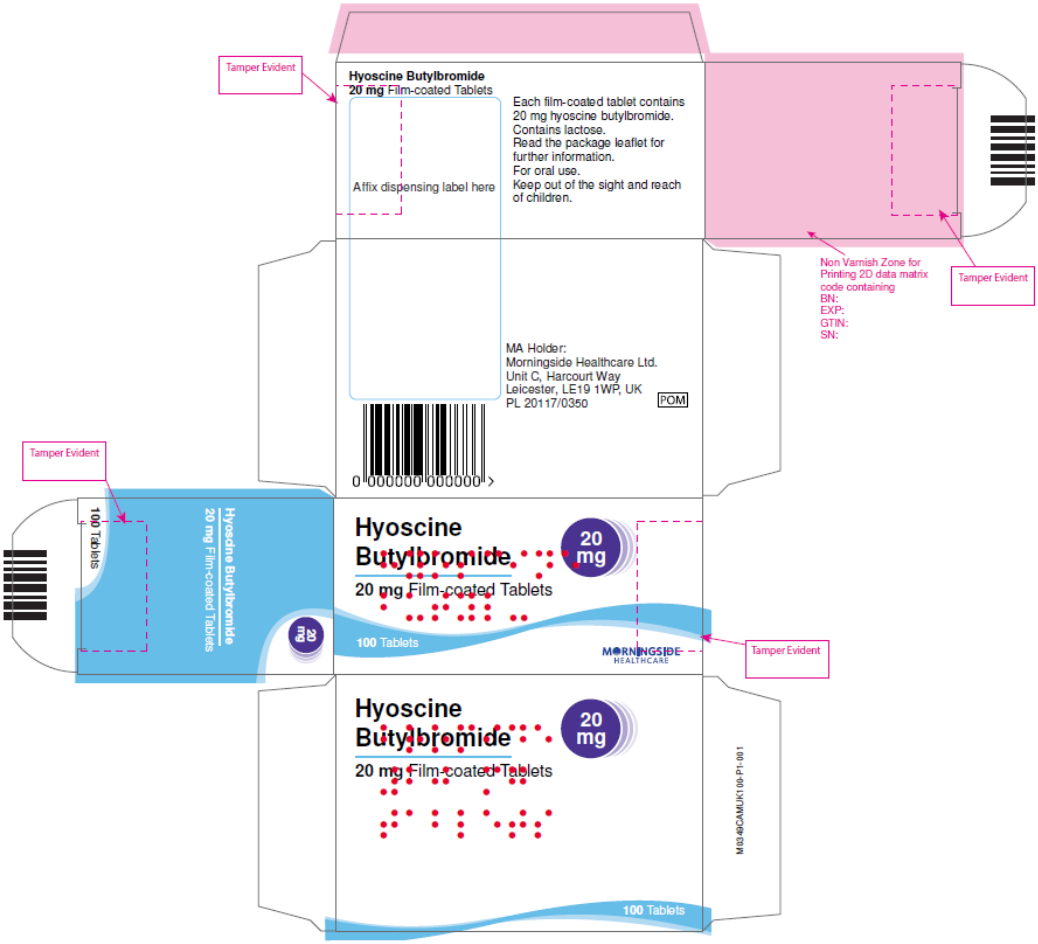
M0349CAMUK100-P1-001
56 Tablets

Hyoscine Butylbromide 20 mg Film-coated Tablets (PL 20117/0350)





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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**