COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gaviscon Duo sachets, oral suspension in sachet (sodium alginate, sodium bicarbonate and calcium carbonate)

NL/H/4535/001

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Gaviscon Duo sachets, oral suspension in sachet. The procedure was finalised in the United Kingdom (UK/H/3493/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

GAVISCON DOUBLE ACTION LIQUID SACHETS PEPPERMINT FLAVOUR 500MG/213MG/325MG ORAL SUSPENSION IN SACHET

(Sodium alginate, sodium bicarbonate and calcium carbonate)

Procedure No: UK/H/3493/001/DC

UK Licence No: PL 00063/0608

RECKITT BENCKISER HEALTHCARE (UK) LIMITED

LAY SUMMARY

Gaviscon Double Action Liquid Sachets Peppermint Flavour 500mg/213mg/325mg Oral suspension in sachet

(Sodium alginate, sodium bicarbonate and calcium carbonate)

This is a summary of the Public Assessment Report (PAR) for Gaviscon Double Action Liquid Sachets Peppermint Flavour 500mg/213mg/325mg Oral suspension in sachet (PL 00063/0608; UK/H/3493/001/DC). For ease of reading, the product will be referred to as 'Gaviscon Double Action Liquid Sachets' in this lay summary.

The lay summary explains how the application for Gaviscon Double Action Liquid Sachets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Gaviscon Double Action Liquid Sachets. For practical information about using Gaviscon Double Action Liquid Sachets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Gaviscon Double Action Liquid Sachets and what are they used for?

Gaviscon Double Action Liquid Sachets is a medicine with 'well-established use'. This means that the medicinal use of the active substances (sodium alginate, sodium bicarbonate and calcium carbonate) of Gaviscon Double Action Liquid Sachets is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Gaviscon Double Action Liquid Sachets are used for the treatment of acid related symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion, for example following meals or during pregnancy.

How do Gaviscon Double Action Liquid Sachets work?

The medicinal product, Gaviscon Double Action Liquid Sachets, is a combination of two antacids (calcium carbonate and sodium bicarbonate) and an alginate (sodium alginate), which works in two ways:

1. Neutralising excess stomach acid to relieve the pain and discomfort.
2. Forming a protective barrier over the stomach contents to soothe the burning pain in the chest which may last for up to 4 hours.

How are Gaviscon Double Action Liquid Sachets used?

Gaviscon Double Action Liquid Sachets is an oral suspension with the odour and flavour of peppermint, which is packaged in sachets. This medicine is taken by mouth (orally).

Gaviscon Double Action Liquid Sachets can be obtained without a prescription, at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist

This medicine should always be taken exactly as described in the package leaflet or as instructed by the patient's doctor or pharmacist. The patient should check with the doctor or pharmacist if he/she is not sure.

Dosage:
Adults including older people and children 12 years and over
10-20 ml (one to two sachets) after meals and before bedtime, up to four times a day.

Children under 12 years old: Should only be taken on medical advice.

Please read the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

What benefits of Gaviscon Double Action Liquid Sachets have been shown in studies?
As calcium carbonate and sodium bicarbonate and sodium alginate are well-known substances and their use in the proposed indication is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of calcium carbonate and sodium bicarbonate and sodium alginate in the proposed indications.

What are the possible side effects of Gaviscon Double Action Liquid Sachets?
Like all medicines Gaviscon Double Action Liquid Sachets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Gaviscon Double Action Liquid Sachets, see section 4 of the package leaflet.

Also, for the full list of restrictions, see the package leaflet for Gaviscon Double Action Liquid Sachets.

Why is Gaviscon Double Action Liquid Sachets approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Gaviscon Double Action Liquid Sachets outweigh the identified risks and recommended that the product be approved.

What measures are being taken to ensure the safe and effective use of Gaviscon Double Action Liquid Sachets?
A Risk Management Plan has been developed to ensure that Gaviscon Double Action Liquid Sachets is 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 Gaviscon Double Action Liquid Sachets, 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/reviewed continuously.

Other information about Gaviscon Double Action Liquid Sachets
Belgium, Cyprus, Czech Republic, Germany, Denmark, Greece, Finland, Hungary, Ireland, Iceland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Sweden, Slovakia and the UK agreed to grant a Marketing Authorisation on 04 October 2012.

A Marketing Authorisation for Gaviscon Double Action Liquid Sachets was granted in the UK to Reckitt Benckiser Healthcare (UK) Limited on 05 December 2012.

The full PAR for Gaviscon Double Action Liquid Sachets follows this summary.

For more information about treatment with Gaviscon Double Action Liquid Sachets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2018.

SCIENTIFIC DISCUSSION

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Scientific Discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Gaviscon Double Action Liquid Sachets Peppermint Flavour 500mg/213mg/325mg Oral suspension in sachet (PL 00063/0608; UK/H/3493/001/DC) could be approved. For ease of reading, the product will be referred to as 'Gaviscon Double Action Liquid Sachets' in this scientific discussion.

This application was submitted by the Decentralised Procedure, with the UK as Reference Member State (RMS), and Belgium, Cyprus, Czech Republic, Germany, Denmark, Greece, Finland, Hungary, Ireland, Iceland, Italy, Luxembourg, Netherlands, Norway, Poland, Portugal, Sweden and Slovakia as Concerned Member States (CMS).

Gaviscon Double Action Liquid is available as a General Sales List (GSL) medicine and is indicated for treatment of acid related symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion, for example following meals or during pregnancy.

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

The medicinal product is a combination of two antacids (calcium carbonate and sodium bicarbonate) and an alginate (sodium alginate).

On ingestion, the medicinal product reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents effectively impeding gastro-oesophageal reflux. In severe cases, the raft itself may be refluxed into the oesophagus, in preference to the stomach contents and exert a demulcent effect.

Calcium carbonate neutralises gastric acid to provide fast relief from indigestion and heartburn. This effect is increased by the addition of sodium bicarbonate which also has a neutralising action. The total neutralising capacity of the product at the lowest dose of 10 ml is approximately 10 $mEqH^+$.

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

Although no new clinical studies were conducted in support of this application, the Marketing Authorisation Holder (MAH) makes reference to a raft formation pharmacodynamic study which was submitted to support the approved application Gaviscon Double Action Liquid (PL 00063/0156). This study contains the same formulation as this application (see III.3 Clinical Aspects). The bridging using this study is accepted.

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

The RMS and CMS considered that the application could be approved, with the end of procedure (Day 210) on 04 October 2012. After a subsequent national phase, the licence was granted in the UK on 05 December 2012.

II QUALITY ASPECTS

II.1 Introduction

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is an off-white suspension, with the odour and flavour of peppermint, packaged in sachets.

Each 10 ml dose (sachet) contains sodium alginate 500 mg, sodium bicarbonate 213 mg and calcium carbonate 325 mg, as active substances. The product also contains pharmaceutical excipients namely, Carbomer 974P, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), saccharin sodium, peppermint flavour, sodium hydroxide and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in unit dose stick pack style sachets composed of heat sealable laminate composed of polyester/aluminium foil/polyethylene/ polyester/polyethylene. The sachets are packaged in cartons, in pack sizes of 4,12 and 24 sachets.

Not all pack sizes may be marketed.

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

II.2 Drug Substance

(1) Calcium carbonate

INN:	Calcium carbonate
Chemical name:	Carbonic acid calcium salt
Molecular formula:	$CaCO_3$
Molecular mass:	100.1
Appearance:	White or almost white powder
Solubility:	Practically insoluble in water.

Calcuim carbonate is currently the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance calcium carbonate are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

(2) Sodium bicarbonate

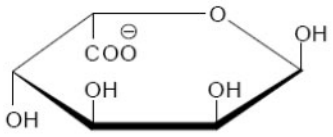
INN:	Sodium bicarbonate, sodium hydrogen carbonate.
Chemical name:	Carbonic acid monosodium salt
Molecular formula:	$NaHCO_3$
Molecular mass:	84.0
Appearance:	White or almost white, crystalline powder
Solubility:	Soluble in water and practically insoluble in ethanol.

Sodium bicarbonate is currently the subject of a European Pharmacopoeia monograph.

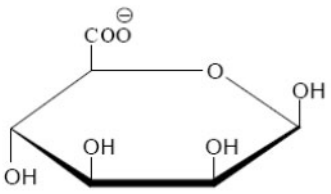
(3) Sodium alginate

INN:	Sodium alginate
Chemical name:	Mixture of D-mannuronic acid and L-guluronic acid
Structure:	

i. Monomers forming Alginates

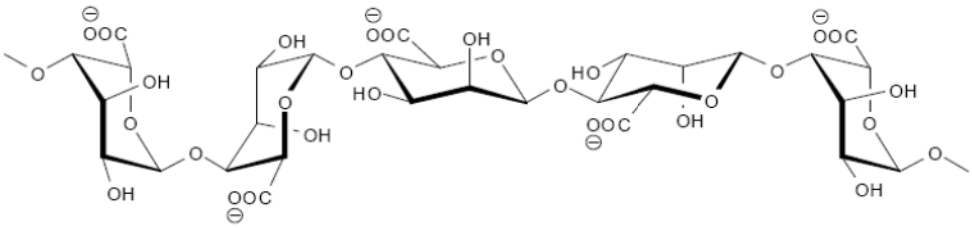


Alpha-L-guluronate (G)



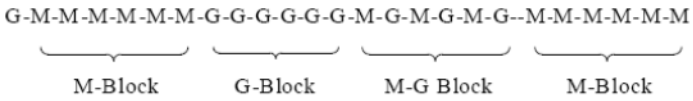
Beta-D-mannuronate (M)

ii. Alginate Polymer



G G M M G

iii. Alginate Polymer Sequence



Molecular formula: $[(C_6 H_7 Na O_6)_n]$
Molecular mass: 20,000 – 600,000
Appearance: White or pale-yellowish-brown powder
Solubility: It slowly dissolves in water forming a viscous, colloidal solution.

Sodium alginate is currently the subject of a European Pharmacopoeia monograph.

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

Appropriate specifications are provided for the active substances. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substances sodium carbonate and sodium alginate. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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

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

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate an oral suspension that provides easy relief from gastric reflux and with an acid neutralising capacity (ANC) equivalent to other Over the Counter (OTC) antacids (ANC ≥ 10 mEq) and to obtain a finished product as similar as possible to Liquid Gaviscon (PL 00063/0031) and with similar shelf-life.

A satisfactory account of the pharmaceutical development has been provided.

With the exception of peppermint flavour, all excipients comply with their respective European Pharmacopoeia monograph. Peppermint flavour is compliant with a suitable in-house specification and is in compliance with Council Directive 88/388/EEC on flavourings for use in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

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 at commercial scale and shown satisfactory results. In addition, the Marketing Authorisation Holder (MAH) has committed to perform additional process validation on future commercial scale batches.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and these comply with the release specification. Certificates of analysis have been provided for all working standards used.

Stability of the Product

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions 'Do not store above 30°C. Do not refrigerate or freeze.'

Bioequivalence/bioavailability

A bioequivalence study was not necessary to support this application. The mode of action of the suspension is physical and not dependant on absorption into the systemic circulation.

Conclusion

There are no objections to the approval of this application, from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of sodium alginate, sodium bicarbonate and calcium carbonate are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

An environmental risk assessment has not been conducted. Due to the nature of its constituents, the product is exempt from the environmental risk assessment (Guideline on the Environmental Risk Assessment of Medicinal products for Human Use).

There are no objections to the approval of this product, from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

The clinical pharmacology of sodium alginate, sodium bicarbonate and calcium carbonate is well known.

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Although no new pharmacodynamic or pharmacokinetic data are provided or required for this application, the MAH makes reference to the following pharmacodynamic raft formation study which was submitted to support the approved application Gaviscon Double Action Liquid (PL 00063/0156). The bridging using this study is accepted:

A randomised, open, three-way crossover study was performed to investigate the formulation and retention of alginate rafts assessed by gamma scintigraphy, in healthy volunteers (males, aged 18-45 years), following administration of single doses of the test liquid (10ml, 500mg sodium alginate) and tablets (2 x 250mg sodium alginate) and liquid Gaviscon (10ml, 500g sodium alginate). An established gamma scintigraphic technique was used. Data was collected at 15 minute intervals over 4 hours and used to derive parameters relating to gastric emptying, etcetera.

The primary efficacy parameter was the gastric retention of the study drug in the whole stomach, which was compared between study drugs using analysis of variance of logtransformed data. Non-inferior gastric retention for the test tablets and liquid in comparison with liquid Gaviscon was to be demonstrated by a de-transformed 95% Confidence Interval (CI) entirely above the non-inferiority limit of 0.8.

From the results, it was deemed that both the test liquid and tablets (x2) had non inferior gastric retention to Gaviscon liquid 10ml.

Efficacy

No new efficacy data were submitted or required for this application.

Safety

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

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

Conclusion

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

V. USER CONSULTATION

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

VI. OVERALL CONCLUSION, BENEFIT-RISK ASSESSMENT AND CONCLUSION QUALITY

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Sodium alginate, sodium bicarbonate and calcium carbonate are well--known active substances. Extensive clinical experience with the actives is considered to have demonstrated the therapeutic value of the product.

The benefit-risk is, therefore, considered to be positive.

The grant of a Marketing Authorisation is recommended.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

The labelling text below is that agreed at the end of the Decentralised procedure. The Marketing Authorisation Holder has committed to submit the labelling mock-ups for review to the regulatory authorities before marketing any pack.

PROPOSED LABEL

1. NAME OF THE MEDICINAL PRODUCT

Gaviscon Double Action Liquid Sachets Peppermint Flavour
500mg/213mg/325mg Oral suspension in sachet
Sodium alginate / Sodium bicarbonate / Calcium carbonate

2. STATEMENT OF ACTIVE SUBSTANCES

Each 10 ml sachet contains sodium alginate 500 mg, sodium bicarbonate 213 mg and calcium carbonate 325 mg.

3. LIST OF EXCIPIENTS

Contains sodium, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).
Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral Suspension in sachet.
4 x 10ml sachets
12 x 10ml sachets
24 x 10ml sachets

5. METHOD AND ROUTES OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER WARNINGS

If symptoms persist after 7 days consult your doctor. Contains sodium and calcium. If you have been advised to follow a diet restricted in either of these salts, please consult your doctor before taking this product.

8. EXPIRY DATE

EXP: MM/YYYY.

Do not use after the expiry date (EXP: month/year shown).

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C . Do not freeze or refrigerate.

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

Medicines should not be disposed of via household wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS. United Kingdom.

12. MARKETING AUTHORISATION NUMBERS

PL 00063/0608

13. BATCH NUMBER

BN _____

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

Adults, including the elderly and children 12 years and over: 10 to 20 ml (1 to 2 sachets) after meals and at bedtime, or as directed, up to four times a day.

Children under 12 years old: Should only be taken on medical advice.

16. INFORMATION ON BRAILLE

Gaviscon Double Action Liquid Sachets Peppermint Flavour
500mg/213mg/325mg Oral suspension in sachet

PROPOSED IMMEDIATE (SACHET) LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gaviscon Double Action Liquid Sachets Peppermint Flavour
500mg/213mg/325mg Oral suspension in sachet
Sodium alginate / Sodium bicarbonate / Calcium carbonate

2. METHOD OF ADMINISTRATION
For oral administration. Adults and children 12 years and over: 10-20 ml (1 to 2 sachets) after meals and at bedtime, up to four times per day.
Children under 12 years: Should be given only on medical advice.
Read the package leaflet before use.

3. EXPIRY DATE
EXP:xxxxxxxx

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>
Lot: xxxxxxxx

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
10ml e

Annex 1 - 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

The following table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
To update section 5.1 of the Summary of Product Characteristics and section 1 of the Patient Information Leaflet in line with available scientific evidence regarding the speed and duration of action of the product, and specific wording relating to the mode of action	UK/H/3493/001/WS/012	SmPC PIL	24/03/2017	06/12/2017	Approval	Yes (Annex 1.1)

Annex 1.1

Our Reference:	PL 00063/0608, Application 0019
Product:	Gaviscon Double Action Liquid Sachets Peppermint Flavour 500mg/213mg/325mg Oral suspension in sachet
Marketing Authorisation Holder:	Reckitt Benckiser Healthcare (UK) Limited
Active Ingredient(s):	Sodium alginate, sodium bicarbonate and calcium carbonate
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Complex
EU Procedure Number (if applicable):	UK/H/3493/001/WS/012

Reason:
To update section 5.1 of the Summary of Product Characteristics (SmPC) and section 1 of the Patient Information Leaflet in line with available scientific evidence regarding the speed and duration of action of the product, and specific wording relating to the mode of action.

Supporting Evidence
Updated clinical overview
Supportive bibliographic references
Revised SmPC fragment
Updated leaflet.

Evaluation
The scientific evidence presented as part of this variation package to support the proposed changes is considered valid.

The proposed changes to the SmPC and leaflet are considered satisfactory.

Conclusion
Based on a review of the supporting documentation submitted, the variation application to update section 5.1 of the SmPC and section 1 of the Patient Information Leaflet is considered approvable. The benefit risk remains unchanged.

The proposed changes to the SmPC and leaflet are considered acceptable.

In accordance with Directive 2010/84/EU the SmPC and PIL for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision
Approved on 05 December 2017.