Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Assicco 1 mg Tablets/Glycopyrronium Bromide 1 mg Tablets

Assicco 2 mg Tablets/Glycopyrronium Bromide 2 mg Tablets

(Glycopyrronium bromide)

PL 20117/0094 - 0095

Morningside Healthcare Limited

LAY SUMMARY

Assicco 1 mg Tablets/Glycopyrronium Bromide 1 mg Tablets
Assicco 2 mg Tablets/Glycopyrronium Bromide 2 mg Tablets

(Glycopyrronium bromide)

This is a summary of the Public Assessment Report (PAR) for Assicco 1 mg and 2 mg Tablets/Glycopyrronium Bromide 1 mg and 2 mg Tablets (formerly Glycopyrronium Bromide 1 mg and 2 mg 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 Glycopyrronium Bromide Tablets in this lay summary for ease of reading.

For practical information about using Glycopyrronium Bromide Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Glycopyrronium Bromide Tablets and what are they used for?
These applications are for medicines that have well-established use. This means that the use of the active substance in these medicines has been well-established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Glycopyrronium Bromide Tablets are used to treat excessive production of saliva (sialorrhoea) in children and adolescents aged 3 years and older. Sialorrhoea (drooling or excessive salivation) is a common symptom of many diseases of the muscles or nerves. It is mainly caused by poor control of muscles in the face. Glycopyrronium Bromide Tablets act on the salivary glands to reduce production of saliva.

How do Glycopyrronium Bromide Tablets work?
The active substance glycopyrronium bromide belongs to a group of medicines known as quaternary ammonium anticholinergics, which are agents that block or reduce the transmission between nerve cells. This reduced transmission can de-activate the cells that produce saliva.

How are Glycopyrronium Bromide Tablets used?
The pharmaceutical form of these medicines is tablets and the route of administration is oral (taken by mouth).

The tablet(s) should be swallowed with water. The tablet(s) may also be halved along the break-line in order to divide the dose into two equal halves.

These medicines should be given at least **one hour before or two hours** after a meal, or at consistent times in relation to food intake. Glycopyrronium Bromide Tablets should not be given with high fat foods.

Use in children and adolescents aged 3 years and older
The initial dose will be calculated based on the weight of the child. The dose will be decided by the doctor using the table below as a guide and will depend on both the effect of Glycopyrronium Bromide Tablets and any side effects the child may have. Section 4 of the

package leaflet includes possible side effects related to the use of Glycopyrronium Bromide Tablets (this is why several dose levels appear in the Table below). These should be discussed with the child's doctor, including the need for dose increases as the child grows, and at any other time should the caregiver be concerned. The child should be monitored at regular intervals (at least every 3 months) to check that Glycopyrronium Bromide Tablets remain appropriate treatment for them.

Weight kg	Dose Level 1 (~0.02 mg/kg)	Dose Level 2 (~0.04 mg/kg)	Dose Level 3 (~0.06 mg/kg)	Dose Level 4 (~0.08 mg/kg)	Dose Level 5 (~0.1 mg/kg)
13-17	0.3 mg	0.6 mg	0.9 mg	1.2 mg	1.5 mg
18-22	0.4 mg	0.8 mg	1.2 mg	1.6 mg	2.0 mg
23-27	0.5 mg*	1.0 mg	1.5 mg	2.0 mg	2.5 mg
28-32	0.6 mg	1.2 mg	1.8 mg	2.4 mg	3.0 mg
33-37	0.7 mg	1.4 mg	2.1 mg	2.8 mg	3.0 mg
38-42	0.8 mg	1.6 mg	2.4 mg	3.0 mg	3.0 mg
43-47	0.9 mg	1.8 mg	2.7 mg	3.0 mg	3.0 mg
≥48	1.0 mg	2.0 mg	3.0 mg	3.0 mg	3.0 mg

* 0.5mg dose can be achieved by taking ½ of a 1 mg tablet.

For doses which cannot be achieved using the tablet formulation, other pharmaceutical forms of glycopyrronium bromide are available.

The maximum recommended dose is 0.1 mg/kg **three times** daily, not to exceed 1.5 - 3 mg per dose based upon weight (for further detail see Table above).

For further information on how Glycopyrronium Bromide Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always receive their medicine exactly as their doctor/pharmacist has advised. The caregiver should check with the patient’s doctor or pharmacist if they are not sure.

What benefits of Glycopyrronium Bromide Tablets have been shown in studies?
As the active substance glycopyrronium bromide has been in clinical use for over 10 years, data were provided in the form of literature references to show that glycopyrronium bromide is a safe and efficacious treatment of excessive production of saliva (sialorrhoea) in children and adolescents aged 3 years and older.

What are the possible side effects of Glycopyrronium Bromide Tablets?
The most common side effects with Glycopyrronium Bromide Tablets (which may affect more than 1 in 10 people) are:
- Dry mouth
- Difficulty in passing stools (constipation)

- Diarrhoea
- Being sick (vomiting)
- Flushing
- Nasal congestion
- Unable to completely empty the bladder (urinary retention)
- Reduced secretions in the chest
- Irritability.

For the full list of all side effects reported with these medicines, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

Why were Glycopyrronium Bromide Tablets approved?
It was concluded that the data provided from literature references had shown that Glycopyrronium Bromide Tablets are effective in the treatment of excessive production of saliva (sialorrhoea) in children and adolescents aged 3 years and older. Furthermore, use of the active substance glycopyrronium bromide in the European Union has shown that it has a recognised efficacy and an acceptable level of safety. The Marketing Authorisation Holder (MAH) submitted a pharmacokinetic study which demonstrated that the 2 mg Glycopyrronium Bromide Tablets are bioequivalent to another glycopyrronium product Cuvposa oral solution 1 mg/5mL, which has recognised efficacy and an acceptable level of safety based on studies in the literature. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

Glycopyrronium Bromide Tablets have been authorised with the condition to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Glycopyrronium Bromide Tablets?"

What measures are being taken to ensure the safe and effective use of Glycopyrronium Bromide Tablets?
A Risk Management Plan (RMP) has been developed to ensure that Glycopyrronium Bromide Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients. In addition to the safety information provided in the Glycopyrronium Bromide Tablets product information, the Marketing Authorisation Holder (MAH) has committed to include educational materials for carers and healthcare professionals to ensure the safe and effective use of Glycopyrronium Bromide Tablets,

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

Other information about Glycopyrronium Bromide Tablets
Marketing Authorisations for Glycopyrronium Bromide Tablets were granted in the UK on 06 February 2014.

The full PAR for Glycopyrronium Bromide Tablets follows this summary.

This summary was last updated in April 2021.

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I INTRODUCTION

Please note that the below scientific discussion consists of the original assessment of these product licences, plus a summary of key post approval changes to improve the accuracy of this Public Assessment Report.

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 Assicco 1 mg and 2 mg Tablets/Glycopyrronium Bromide 1 mg and 2 mg Tablets (formerly Glycopyrronium Bromide 1 mg and 2 mg Tablets; PL 20117/0094 - 0095) could be approved.

The products were initially approved on 06 February 2014, for use in adults as add-on therapy in the treatment of peptic ulcer. In July 2018, the Commission of Human Medicines (CHM) recommended the revocation of this indication, on the grounds of insufficient evidence of efficacy.

On 18 March 2021, the products were approved for a new indication of symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders (refer to Annex 2 at the end of this report).

The active ingredient, glycopyrronium bromide, is a quaternary ammonium antimuscarinic agent. Its effects are similar to those of atropine. Antimuscarinic drugs are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves.

The initial applications were submitted under Article 10a of Directive 2001/83/EC, as amended, as well-established use applications. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

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.

National Marketing Authorisations were granted in the UK on 06 February 2014.

Summary of key post approval changes

1. To update sections 4.2 and 6.6 of the SmPCs to add an additional method of administration (PL 20117/0094-0004 and PL 20117/0095-0004 granted 21 March 2016).
2. To add an invented name, Assicco 1 mg Tablets/Assicco 2 mg Tablets to the licences. Consequently, sections 1, 3, 4.2, 4.4, 4.6, 4.7 and 4.8 of the SmPCs, label and PIL have been updated. The label and PIL mock-ups have been approved. (PL 20117/0094-0008 and PL 20117/0095-0008 granted 24/01/2018).
3. To introduce a change in therapeutic indication for Assicco 1 mg and 2 mg Tablets/Glycopyrronium Bromide 1 mg and 2 mg Tablets, following a Commission of Human Medicines (CHM) referral which determined that the efficacy data supporting the Marketing Authorisations (MAs) are insufficient to establish the efficacy of glycopyrronium as add-on therapy in the treatment of peptic ulcer in adults. The new indication is ‘symptomatic treatment of severe

sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older.' Consequently, sections 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPCs, the PIL and the Risk Management Plan (RMP) have been updated. (PL 20117/0094-0015 and PL 20117/0095 0015 granted 18/03/2021).

To note: the main body of this report (lay summary and introduction sections) has been updated with this important new indication change. Please also refer to Annex 2 at the end of this PAR for further details.

II QUALITY ASPECTS

II.1 Introduction

These products consist of 1 mg or 2 mg glycopyrronium bromide in each tablet.

In addition to glycopyrronium bromide, these products also contain the excipients lactose monohydrate, dibasic calcium phosphate, povidone, sodium starch glycolate and magnesium stearate.

The finished products are packaged in aluminium blisters of 10, 14, 28, 30, 56, 60, 90 and 112 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.

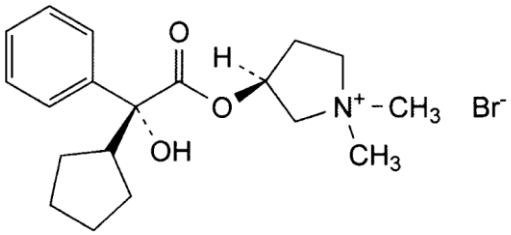
II.2 ACTIVE SUBSTANCE

rINN: **Glycopyrronium Bromide**

Chemical Name: (3*RS*)-3-[(2*SR*)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide

Molecular Formula: $C_{19}H_{28}BrNO_3$

Chemical Structure:



and enantiomer

Molecular Weight: 398.3 g/mol

Appearance: White or almost white crystalline powder

Solubility: Freely soluble in water, soluble in ethanol (96%) and very slightly soluble in methylene chloride.

Glycopyrronium bromide is the subject of a European Pharmacopoeia monograph.

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

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

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

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

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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, none of the excipients contain material of animal or human origin. 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 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

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, a well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology

No new pharmacology data were submitted, and none were required for these applications.

III.3 Pharmacokinetics

No new pharmacokinetic data were submitted, and none were required for these applications.

III.4 Toxicology

No new toxicology data were submitted, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

A revised ERA has been submitted post-authorisation, as part of the variations PL 20117/0094-0015 and PL 20117/0095-0015 (granted 18/03/2021) for a change in indication. Please refer to Annex 2 at the back of this report for the assessment of the MAH's current approved ERA.

III.6 Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

IV. 2 Pharmacokinetics

No new pharmacokinetic data have been submitted for these applications and none were required.

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 have been submitted for these applications and none were required.

IV.5 Clinical safety

No new safety data were submitted with these applications and none were required. Safety is adequately reviewed in the clinical overview. The safety profile of glycopyrronium bromide is well-known.

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 Patient Information Leaflet (PIL) 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 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 from the literature. Extensive clinical experience with glycopyrronium bromide 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 Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

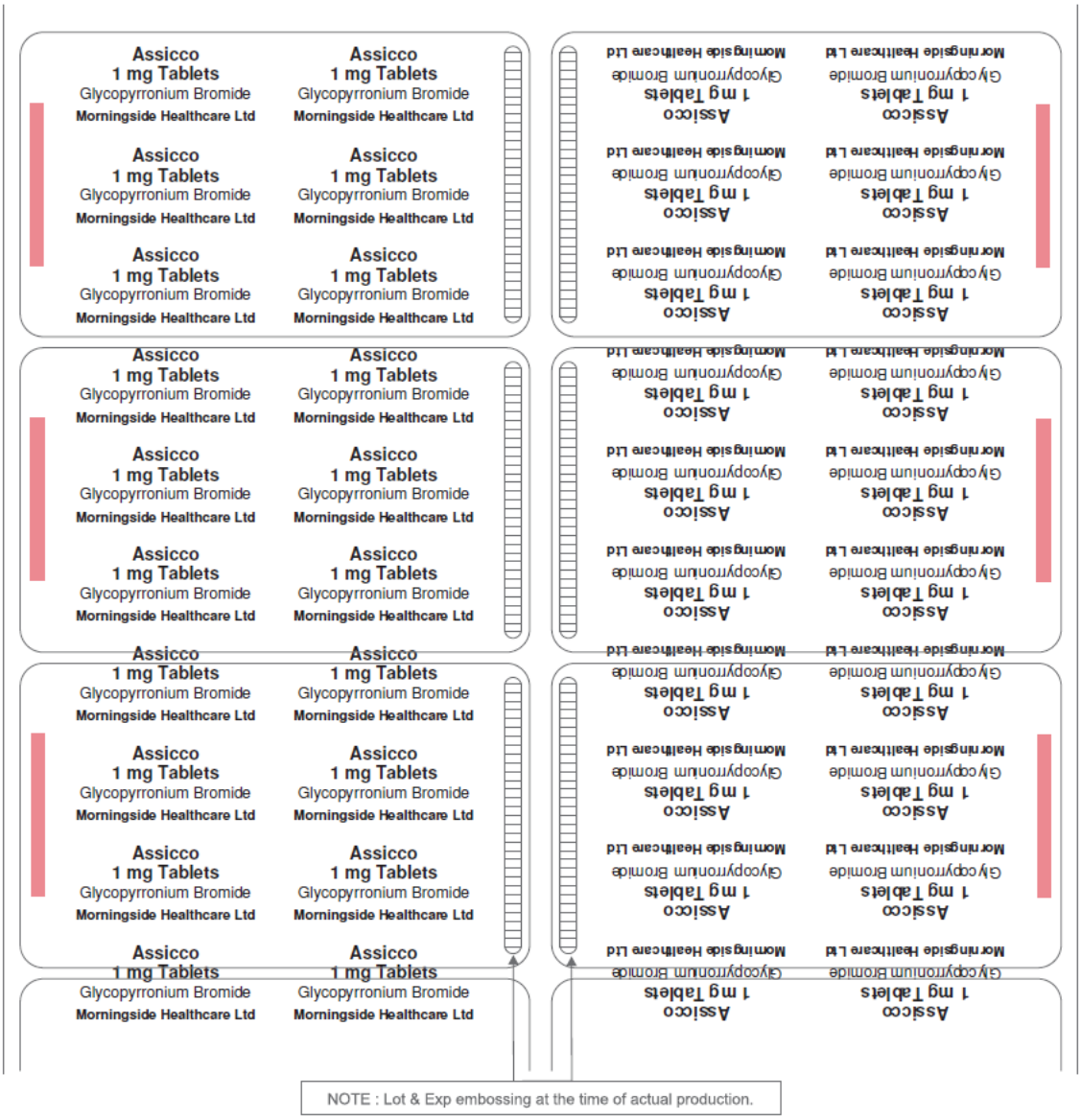
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

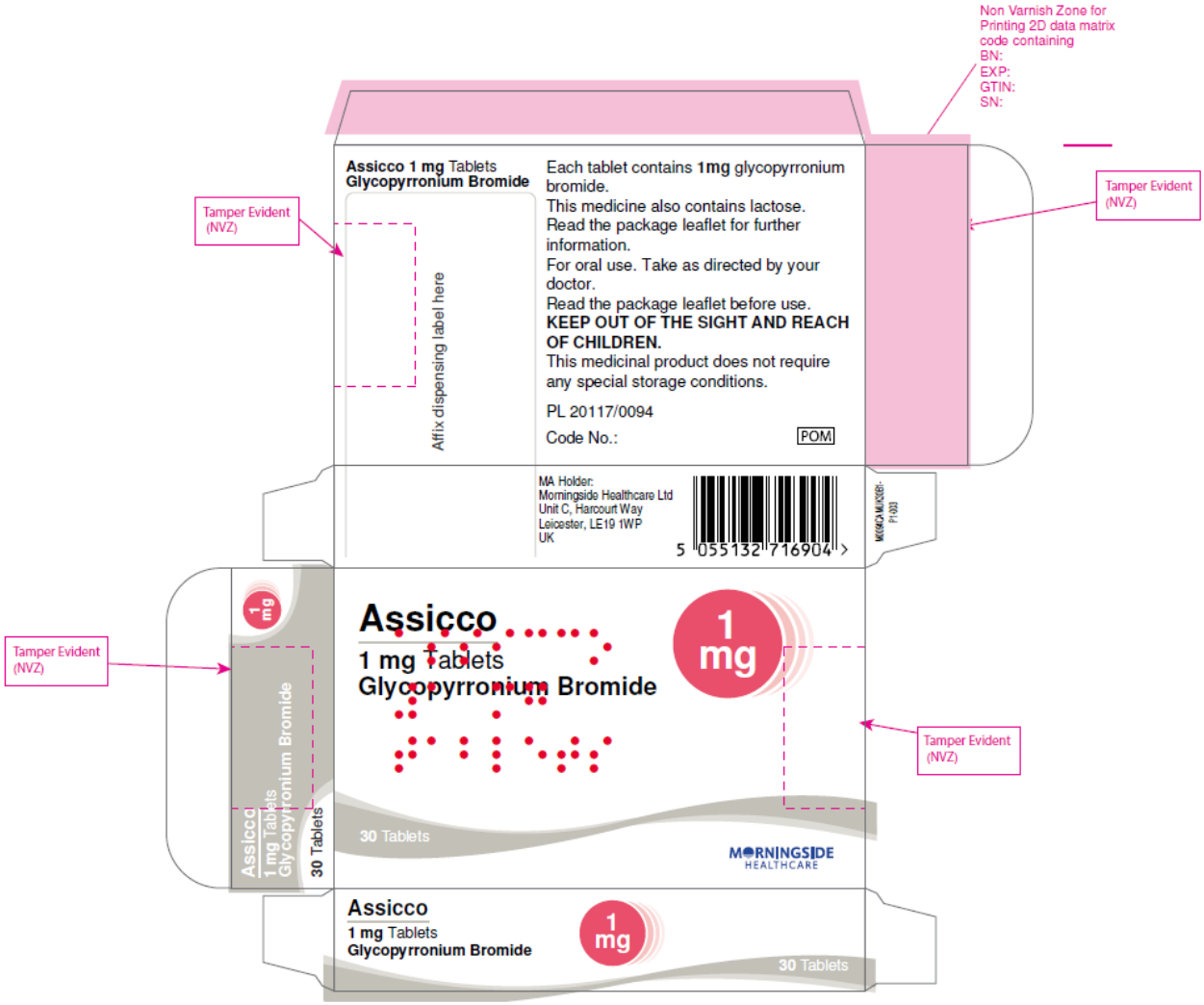
Representative copies of the labels at the time of UK licensing are provided below.

Glycopyrronium Bromide 1 mg Tablets

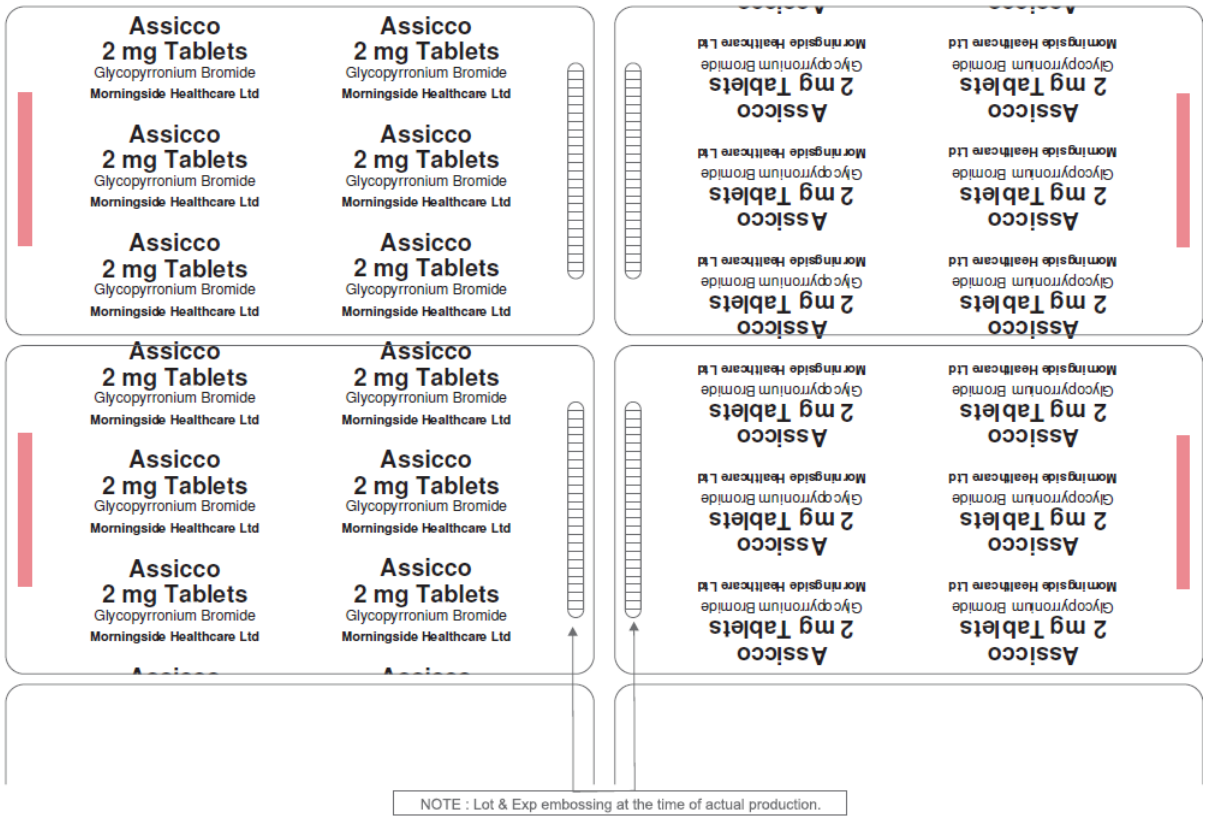
Glycopyrronium Bromide 2 mg Tablets

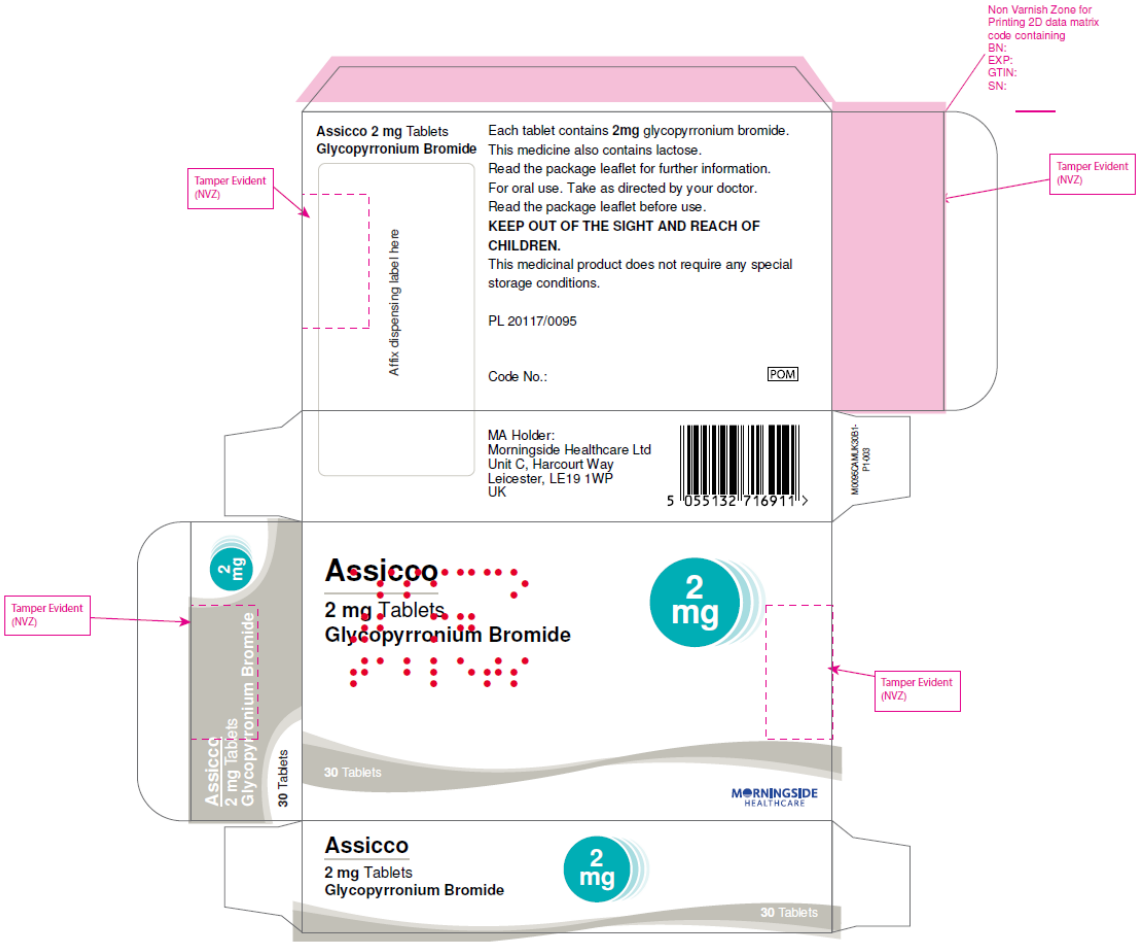
Assicco 1 mg Tablets




Non Varnish Zone for Printing 2D data matrix code containing
BN:
EXP:
GTIN:
SN:
Tamper Evident (NVZ)
Tamper Evident (NVZ)
Tamper Evident (NVZ)
Tamper Evident (NVZ)
Assicco 1 mg Tablets
Glycopyrronium Bromide
Each tablet contains 1mg glycopyrronium bromide.
This medicine also contains lactose.
Read the package leaflet for further information.
For oral use. Take as directed by your doctor.
Read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
This medicinal product does not require any special storage conditions.
PL 20117/0094
Code No.:
POM
Affix dispensing label here
MA Holder:
Morningside Healthcare Ltd
Unit C, Harcourt Way
Leicester, LE19 1WP
UK
5 055132 716904
Assicco
1 mg Tablets
Glycopyrronium Bromide
1 mg
30 Tablets
MORNINGSIDE HEALTHCARE

Assicco 2 mg Tablets




Non Varnish Zone for Printing 2D data matrix code containing
BN:
EXP:
GTIN:
SN:
Tamper Evident (NVZ)
Tamper Evident (NVZ)
Assicco 2 mg Tablets
Glycopyrronium Bromide
Each tablet contains 2mg glycopyrronium bromide.
This medicine also contains lactose.
Read the package leaflet for further information.
For oral use. Take as directed by your doctor.
Read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
This medicinal product does not require any special storage conditions.
Affix dispensing label here
PL 20117/0095
Code No.:
POM
MA Holder:
Morningside Healthcare Ltd
Unit C, Harcourt Way
Leicester, LE19 1WP
UK
5 055132 716911
Assicco
2 mg Tablets
Glycopyrronium Bromide
2 mg
30 Tablets
MORNINGSIDE HEALTHCARE
Tamper Evident (NVZ)
Tamper Evident (NVZ)

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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 authorisations 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**
Type II	To update sections 4.2 (Posology and method of administration) and 6.6 (Special precautions for disposal) of the SmPCs to add an additional method of administration	SmPC	21/03/2016	Approved	Yes (Annex I)
Type II	To introduce a change in therapeutic indication for Assicco 1 mg and 2 mg Tablets/Glycopyrronium Bromide 1 mg and 2 mg Tablets, following a Commission of Human Medicines (CHM) referral which determined that the efficacy data supporting the MAs are insufficient to establish the efficacy of glycopyrronium as add-on therapy in the treatment of peptic ulcer in adults. The new indication is 'symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older.' Consequently, sections 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPCs, the PIL and the Risk Management Plan (RMP) have been updated.	SmPC PIL RMP	18/03/2021	Approved	Yes (Annex 2)

ANNEX 1

Our Reference:	PL 20117/0094-0004 PL 20117/0095-0004
Products:	Glycopyrronium Bromide 1 mg Tablets Glycopyrronium Bromide 2 mg Tablets
Marketing Authorisation Holder:	Morningside Healthcare Limited
Active Ingredient(s):	Glycopyrronium Bromide
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Standard
EU Procedure Number (if applicable):	Not applicable

Reason:
To update sections 4.2 and 6.6 of the SmPCs to add an additional method of administration.

Supporting Evidence
Quality overall summary (QOS), clinical overview, curriculum vitae (CV) of the quality expert, revised SmPC fragments.

Glycopyrronium Bromide 1 mg tablet (PL 20117/0094) and Glycopyrronium Bromide 2 mg tablet (PL 20117/0095) were introduced to the UK market in July 2014. Following the introduction, it became evident that there was a large usage, or requirement for usage, within the National Health Service (NHS), for dispersion/solubilisation of the tablets in water, and subsequent administration either as an oral dispersion where oral tablet administration was impracticable (i.e. dysphagia), or via a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) tube, on the basis of documented medical enquiries received by the Marketing Authorisation Holder (MAH). Such usage cannot be recommended by the MAH, since these routes of administration are currently unlicensed.

The MAH has therefore decided to seek authorisation for such administration, as an exceptional case where oral administration of the tablet is undesirable/impracticable, by means of a variation to the marketing authorisations.

Evaluation
Clinical evaluation:
Proposed change to section 4.2 posology and method of administration
The MAH proposes adding the text:
"In exceptional instances it may not be possible to administer the tablets orally, please refer to recommendations in section 6.6 of the SmPC for administration as an extemporaneous dispersion orally. This method is also suitable for administration via nasogastric tube or percutaneous endoscopic gastrostomy (PEG) tube."

Proposed change to section 6.6 Special precautions for disposal and other handling of the product
The MAH proposes adding the text:

"For patients where oral administration of tablet is not possible, or not desired, administration by tablet solubilisation, and subsequent administration as an extemporaneous oral dispersion, or by administration via a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) tube. Such dispersions should be administered as suggested following. For dosage recommendations see section 4.2 previously.
Dispersions of a tablet, either 1 mg or 2 mg, is done as follows, use water as a dispersant medium and a 60 ml oral syringe as the vessel for dispersion.

- Remove the plunger from the syringe and introduce a single tablet into the syringe barrel, replace the plunger and depress to just above tablet
- Draw up the required volume of water, either potable or purified is suitable, a volume of 10 ml to 30 ml is recommended, dependent upon any patient fluid intake restrictions, and manually shake the syringe assembly for 30 seconds
- Allow to stand for 5 minutes and manually shake for another 30 seconds
- Allow to stand for a further 5 minutes and manually shake for another 30 seconds
- Allow to stand for a further 5 minutes and manually shake for another 30 seconds

The tablet dispersion should be administered immediately after preparation. The dispersion is opaque, with some visible heavy particulates that are an inactive ingredient. The whole of the dispersion, including residue, is to be administered.

The studies conducted with the nasogastric and PEG tubes evaluated three types of tubing, polyvinylchloride, polyurethane and silicone, which concluded that there were no significant differences evident between the three types of tubing and showed satisfactory corresponding overall recovery levels. Similarly, filtration studies prior to analysis performed to evaluate if undissolved residues contained significant amounts of glycopyrronium bromide, concluded that there was no significant decrease in amount recovered. Filtered and unfiltered samples both showed acceptable equivalent overall recoveries.
Administration may be by the following routes:

- Administration orally, as an aqueous dispersion. Following administration of the dispersion, the oral syringe is rinsed with a further quantity of water, a minimum of 10 ml, that should also be taken to ensure complete dosing
- Administration via either a nasogastric tube, or by a PEG tube. Tubes made of polyvinylchloride, polyurethane, or silicon are suitable. There is no data available on tubes made of latex; such tubes should not be used. Immediately following administration of the initial dispersion, by connection of the oral syringe to the tube, the oral syringe is disconnected and rinsed with a further 10 ml of water, which should also be administered, in order to ensure complete dosing.

Such dispersions should not be used to provide doses below that of the tablet used to prepare the dispersion, since there is no data available to support such dose subdivision. Dispersion should be administered immediately following preparation. There is no data available to show that the medicine could be co-administered with food when administered through enteral tubes."

Satisfactory documented evidence, from various types of health care providers, enquiring about the possibility of alternative administration through PEG or nasogastric tube was submitted. Such usage cannot be recommended by the MAH, since these routes of administration are currently unlicensed. The updated clinical overview providing the justification has been submitted. The revised QOS has also been submitted.

The MAH has summarised within the updated clinical section of the dossier a body of evidence which addresses aspects of off label administration of medication including dispersions/solutions of tablets for administration via an oral syringe, or via nasogastric or PEG tube. This includes guidance from UK sources, including widespread official NHS guidance and recommendations. On the basis of this guidance and its distribution throughout the NHS it is clear there is a large clinical and patient requirement for dispersion of oral tablets for enteral tube administration. Specifically, to glycopyrronium bromide, the MAH offers evidence of enquiries made by clinical and nursing staff to its offices on the subjects of tablet crushing and dispersal. Such enquiries totalled approximately 42 % of all medical enquiries received.

The MAH also documents that requests for this information come from community pharmacies, residential care homes, GP practices, the National Pharmacy Association and the PrescQIPP NHS programme, as well as listing 24 NHS Trusts or Clinical Commissioning Groups. This evidence is sufficient to justify the clinical need for dispersal of glycopyrronium bromide tablets and administration by way of enteric tubes.

Quality evaluation

Much of the pharmaceutical data in support of these variations has already been submitted and deemed satisfactory and is already included in the authorised registration dossiers.

The tablets, irrespective of strength, demonstrate rapid disintegration, and rapid dissolution. They are thus, from a physicochemical aspect, suitable for consideration to be used to produce an extemporaneous aqueous dispersion, suitable for oral administration, administration by a nasogastric tube, or administration by a PEG tube, which are all off-licence routes of administration currently in use within the NHS, and subject to official NHS guidance. Therefore, the question of extent of solubilisation, volume of water for solubilisation, and attendant stability was addressed in the submitted additional work.

The analytical procedure used for determination of assay was the validated HPLC dissolution method, as authorised. Due to the concentrations resulting for analysis, i.e. a maximum of 80 microgram/ml, and a minimum of 4 microgram/ml glycopyrronium bromide, it was not possible to analyse the resultant solutions for related substances, due to limit of quantitation restrictions.

This is considered acceptable while demonstrating both content and solution stability, since the analytical procedure has been determined to be stability-indicating, during both validation and stress degradation studies, as already included and assessed in the dossier.

The experiment was conducted on sufficient replicates, for each strength, 1 mg tablet and 2 mg tablet, and evaluated significant variables, including volume for dispersion, holding times. All experimentation and sample holding and analysis were done at room temperature, i.e. 20°C to 26°C. All instrumentation and analytical equipment were suitably calibrated and qualified, as appropriate. Routine production batches were used for testing. All tablets met the predefined requirements, irrespective of time interval, or of volume of water used for dissolution. There is no evidence for any systematic degradation of the glycopyrronium content with time, nor evidence of concentration dependent stability issues, and therefore tablets dissolved in potable water retain their potency in solution for at least 48 hours.

The recommended 15-minute time for dispersion would seem appropriate and to have an adequate safety margin on the basis of the presented data.

Despite the stability of the resultant solution being satisfactory for up to 48 h, it is proposed that the instructions will stipulate "solutions should be freshly prepared, i.e. administration should occur immediately following the prescribed dissolution period of 15 minutes". This is to provide an adequate safeguard against microbial contamination and proliferation and is also in agreement with existing NHS guidance for this currently unlicensed route of administration and will therefore be familiar to NHS personnel.

The preparation applies to both nasogastric tubes and PEG tubes which are available in various materials of construction, commonly, polyvinylchloride, polyurethane, silicone, and latex. The MAH submitted a study to evaluate if there was any significant interaction between a dispersion of Glycopyrronium Bromide Tablets and the materials of construction used in nasogastric and PEG tubes. In practice, latex tubes tend not to be used, due to clinical concerns over potential latex sensitivity, and proved to be unavailable commercially, and were therefore excluded. The following tubes were evaluated:

- Polyvinylchloride
- Polyurethane
- Silicone

There are no significant differences evident between the three types of tubing that were evaluated in the study, all gave equivalent results. Similarly, filtration prior to analysis, which was being done primarily to evaluate if undissolved residues contained significant amounts of glycopyrronium bromide, does not result in a significant decrease in amount recovered.

It is evident that compared to the results obtained immediately following dispersion in a syringe, there is a drop in the amount of glycopyrronium bromide recovered immediately following dispersion, subsequent to passage through the tubes, in general this is a consistent clinically acceptable level of the administered dose. This is most likely attributable to some degree of adsorption of the active moiety onto the plastic tubes, and evidently to a marginally greater extent than to the syringe material itself.

There is no evidence for any subsequent decrease of glycopyrronium bromide as a result of prolonged contact time with the tubes in the period of evaluation, 60 minutes, which may indicate a saturation effect of adsorption. However, in any use of these systems for administration it would be a rapid and dynamic administration, immediately followed by a flush through with water.

Some of adsorbed glycopyrronium bromide can be recovered by the subsequent use of a water flush, resulting in a slightly enhanced overall recovery for glycopyrronium bromide in a clinically acceptable range.

The tubes used differed in their lengths, polyvinylchloride tube was 100 cm, polyurethane tube was 120 cm, and silicone tube was 125 cm in length, which would result in differing surface areas of exposure for the dispersed tablets, however, there does not appear to be a clear relationship or significant influence attributable to this factor.

It is concluded that using the recommended dispersion method for glycopyrronium bromide tablets, with immediate administration via a nasogastric or PEG tube constructed from polyvinylchloride, polyurethane, or silicone, and with an immediate post administration water flush of the tube, will result in a clinically acceptable percentage of the labelled claim of the dose being delivered to the patient.

A satisfactory justification in respect of clinical effectiveness, addressing physicochemical, regulatory, and biopharmaceutical aspects was submitted.

On the above basis it is considered that a therapeutically effective dose would be administered using a dispersed tablet, given via either a nasogastric or PEG tube made of polyvinylchloride, polyurethane, or silicone, followed by a post administration flush with water.

Conclusion (clinical and quality)
In summary, the evidence presented by the MAH is considered satisfactory. Clinical justification for the proposed amendment to the posology is accepted. On the data provided, it is considered that a therapeutically effective dose would be administered using a dispersed tablet, given via either a nasogastric or PEG tube made of polyvinylchloride, polyurethane, or silicone, followed by a post administration flush with water.

The changes to the SmPC are adequate and justified. The MAH has adequately justified reasons for not updating the PIL with additional administration details on the grounds that it may cause confusion to the vast majority of patients prescribed the product as the additional route of administration will be used only by a very small number of patients, and initial use will be in a hospital environment under direct supervision of a healthcare professional where reference to the SmPC is the most appropriate. If following discharge, the patient is expected to self-administer, then appropriate instruction will be given by the healthcare professional.

The proposed changes to the SmPCs are acceptable. The updated SmPC fragments have been incorporated into the Marketing Authorisations.

Decision- Approved on 21 March 2016.

Annex 2

Reference: PL 20117/0094-0015
PL 20117/0095-0015

Products: Assicco 1 mg Tablets/Glycopyrronium Bromide 1 mg Tablets
Assicco 2 mg Tablets/Glycopyrronium Bromide 2 mg Tablets

Type of Procedure: National

Submission category: Type II Variation (Extended)

Reason
To introduce a change in therapeutic indications for Assicco 1 mg and 2 mg Tablets/ Glycopyrronium Bromide 1 mg and 2 mg Tablets, following a Commission of Human Medicines (CHM) referral which determined that the efficacy data supporting the MAs are insufficient to establish the efficacy of glycopyrronium as add-on therapy in the treatment of peptic ulcer in adults. The new indication is symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older. Consequently, sections 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPCs, the PIL and the Risk Management Plan (RMP) have been updated.

Supporting evidence
The MAH has submitted updated:

- SmPCs
- SmPC fragments
- PIL
- RMP
- 2-4-non-clinical overview
- 2-5-clinical overview
- 2-7-clinical summary
- A comprehensive bibliography (module 5)

In addition, the MAH has submitted:

- a tablet sub-division study as per Ph. Eur.
- a pharmacokinetic bridging study.

Background
Glycopyrronium bromide is a quaternary ammonium antimuscarinic agent that competitively inhibits acetylcholine receptors resulting in a variety of parasympatholytic effects.

The MAH's Glycopyrronium Bromide 1 mg and 2 mg Tablets were approved in 06 February 2014 through the National Procedure under Article 10a of Directive 2001/83/EC, as amended, with the indication: '*Use in adults as add-on therapy in the treatment of peptic ulcer*'. On 19 July 2018, the CHM recommended the revocation of this indication, on the grounds of insufficient evidence of efficacy.

In this Type II Variation, the MAH proposes to remove the peptic ulcer indication and add the following indication: Symptomatic treatment of severe sialorrhoea (chronic pathological

drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older, with consequential changes to the PIL and SmPCs. The Risk Management Plan has also been updated.

Advice was sought from the Commission of Human Medicines (CHM) on 23 May 2019, because major objections were raised with respect to non-clinical and clinical aspects of the dossier. The Committee provisionally concluded that further information on the non-clinical and clinical aspects should be requested before the products could be approved. In response to the CHM advice, the MAH provided further data including a clinical pharmacokinetic study (bioequivalence data including suitable biowaiver data for the 1mg strength) to support the requested indication and posology. The information provided was adequate and the issues were resolved and the variations granted on 18 March 2021.

Evaluation

Quality Evaluation

The MAH submitted supportive data to demonstrate that the tablet can actually be divided into equal halves.

The updated SmPCs and PIL information are considered acceptable from a quality perspective.

Non-clinical Evaluation

The MAH has submitted a revised non-clinical overview in line with the proposed indication of "Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders". A summary of the revised non-clinical overview is provided below. Suitable justification for the absence of non-clinical summaries has been provided.

Pharmacology

Glycopyrronium is a nonselective antagonist of muscarinic cholinergic receptors. Glycopyrronium binds to human and guinea pig airway M_1, M_2, M_3, and M_4 muscarinic receptors with high affinity without demonstrating selectivity. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia.

Anticholinergics (M_3) are effective antisialogogues in monogastrics. In ruminants, however, salivation is not inhibited completely; rather, the saliva becomes more viscous to the point where the thickened, ropy saliva may pose a risk of causing airway obstruction.

The effect of aclidinium, glycopyrronium and tiotropium on salivation was assessed in conscious rats (n = 6-24) that were fasted for 18 hours (with water *ad libitum*) prior to administration of aclidinium (0.1 - 1000 mg/kg, subcutaneously), glycopyrronium (0.1 – 10 mg/kg, subcutaneously), tiotropium (0.1 - 00 mg/kg, subcutaneously) or vehicle subcutaneously in the intercapular area. After 30 minutes, pilocarpine (0.5 mg/kg) was administered via the caudal vein. The presence of any excess saliva was recorded during the first 15-minutes post-pilocarpine administration by gently pressing filter paper on the animal's snout. All three compounds inhibited sialorrhea in a dose-dependent manner. ED_{50} = 38, 0.88 and 0.74 mg/kg for aclidinium, tiotropium and glycopyrronium respectively.

Antisialagogue effect of glycopyrrolate was evaluated in rats. In order to determine the bronchoprotective and antisialagogue potency after a single dose, rats were exposed by inhalation to a nebulised solution of glycopyrrolate (1–1000 mg/ml), or vehicle (sterile water).

For the antisialagogue effect, inhibition of pilocarpine was assessed 1, 6, or 12 hours after inhalation of an efficacious dose of test compound to determine the time point at which peak effect occurred. To evaluate the effect of repeated exposure, animals were exposed by inhalation to seven once-daily doses of glycopyrrolate (1–1000 mg/ml), or vehicle (sterile water). The peak antisialagogue effect of glycopyrrolate (1000 mg/ml) was determined to occur at 1 hour after dosing. At this time point, its antisialagogue potency following a single dose (ID_{50} = 228.2 mg/ml) was not significantly different from its potency after seven daily doses (ID_{50} = 384.2 mg/ml).

The effect of glycopyrrolate on methacholine-stimulated salivary secretion was measured in dogs following intravenous administration. As shown in Table 1, glycopyrrolate was capable of diminishing the volume of salivary secretion, which was stimulated by methacholine.

Table 1. Inhibitory effect of glycopyrrolate on methacholine-stimulated salivary secretion in the dog

Compound	IV dose µg/kg	Time of dose min	Volume of salivary secretion per 10 min ml
Methacholine chloride	11	- 30	0.60
		- 30	0.60
		- 30	0.60
Glycopyrrolate Br	5	0	
Methacholine chloride	11	+10	0.28
		+20	0.37
		+30	0.48
		+40	0.19
		+50	0.20

Six groups of rabbits (n=5-5) received an intramuscular injection of either saline, atropine (0.2 mg/kg), atropine (2 mg/kg), glycopyrrolate (0.1 mg/kg), ketamine:xylazine (35:10 mg/kg) or glycopyrrolate:ketamine:xylazine (0.1:35:10 mg/kg). Salivary secretions were only reduced in glycopyrrolate-treated rabbits.

Motility of the digestive tract and the urinary tract, and salivary secretory activity were measured in dogs. Salivary secretion was recorded by means of an open, fluid-filled system having at one end a (hypodermic) needle-tipped polyethylene tube attached to a glass tubing. The needle-tipped portion of the polyethylene tubing was inserted in Wharton's duct. Glycopyrrolate (8 µg/kg) significantly reduced the methacholine-stimulated salivary secretion.

Atropine, glycopyrrolate, or saline solution was administered before anaesthesia in a blinded, controlled study of 40 dogs (15 males, 25 females) scheduled to undergo surgery. An arbitrary grade was assigned to moistness of the oral mucous membranes: 0 = dry mucous membranes, 1 = moist mucous membranes, and 2 = excessive salivation. The salivary grade was not affected by administration of atropine or glycopyrrolate. The authors acknowledge that the lack of effect on salivation may be an accurate finding or it may reflect inexactness of the subjective evaluation method used.

Only mammals have sweat glands. Most mammals, however, such as cats, dogs, mice, etc., do not have large numbers of sweat glands like humans do. Apart from humans, only few animals - such as apes/monkeys and horses - can evaporate heat through activating eccrine sweat glands. The effects of glycopyrrolate and atropine were compared in ameliorating the adverse effects of imidocarb dipropionate in a blinded, randomised, crossover study performed in 8 healthy horses. Each horse received 0.9% saline IM and IV, and imidocarb 2.4 mg/kg, IM with one of 3 treatments IV: 0.9% saline, atropine 0.02 mg/kg and glycopyrrolate 0.0025 mg/kg. Imidocarb is a carbamate that reversibly inhibits cholinesterase activity. Adverse effects after imidocarb administration include depression, mild to severe colic, diarrhoea, sweating, salivation, lacrimation, miosis, dyspnoea and recumbency. Glycopyrrolate prevented imidocarb-induced sweating of horses.

Pharmacokinetics

Absorption of radiolabelled glycopyrronium (4.83 μCi/mouse), given orally, was evaluated in mice. Only small amounts of radioactivity were detected in the blood 0.5 hours after the oral administration of radiolabelled glycopyrronium and remained detectable in blood up to 6 hours post-dose. When administering radiolabelled glycopyrronium intravenously to mice (0.966 μCi/mouse), peak radioactivity was reached 5 to 10 minutes after injection. Absorption of glycopyrronium, given orally, is poor, probably due to the highly ionised and water-soluble nature of glycopyrronium, with 1.9% of the glycopyrronium dose found in the stomach and 6.4% in the small intestine at 3 hours post-dose.

In a 13-week repeat-dose study in mice, glycopyrronium was administered orally once daily at doses of 30, 100 or 300 mg/kg/day. Values for the C_{max} and the AUC varied widely, which is expected given the low oral bioavailability. In general, exposure was reported to increase with increasing doses and C_{max} and AUC_{last} values were in the range of 1-100 ng/mL and 10–100 h.ng/mL, respectively. However, no C_{max} and AUC values were reported for the highest applied dose of 300 mg glycopyrronium/kg/day. In another 13-week repeat-dose study in rats, oral doses of 40, 120 or 360 mg glycopyrronium/kg/day, were administered once daily over a period of 84 days. C_{max} and AUC values ranged from 3 ng/mL and 9 h.ng/mL, respectively, at the lowest to 1153 ng/mL and 2014 h.ng/mL glycopyrronium at the highest dose administered, with a clear dose dependent increase observed.

The distribution of radiolabelled glycopyrronium administered to mice orally or intravenously was rapid throughout the body and radioactivity was observed in highly perfused tissues (kidney, liver, small intestine and various glands), but not the brain. After multiple oral administrations to mice (3.86 μCi/mouse/day for 7 days) radioactivity in organs was not observed by 72 hours after the last dose. Radiolabelled glycopyrronium was also administered intravenously to pregnant mice and no radioactivity was detected in the foetus. Several tissues in mice (eye, brown fat, Harderian gland, kidney and liver) displayed very slow elimination following intravenous route of administration.

Plasma protein binding of glycopyrronium was tested in different species (mice, rats, rabbits, dogs, and humans). Overall, plasma protein binding was weak without significant differences between species. In these species, protein-binding values ranged from 23-44%. Protein binding values determined in Göttingen minipigs and humans ranged from 24% to 45% for glycopyrronium concentrations of 0.0799 ng/mL, 7.99 ng/mL and 799 ng/mL [0.1, 10 and 1000 ng/mL glycopyrronium bromide]. Values for rabbits and humans tend to be higher than for the other tested species. The blood/plasma concentration ratios were comparable between species (0.48–0.67) with no apparent concentration dependency.

The *in vitro* metabolism of glycopyrronium has been investigated in hepatocytes of various species (mouse, rat, rabbit, dog, and human) and in liver and lung microsomes obtained from rat, dog and human. Only quantitative not qualitative differences were observed between species, and no unique human metabolites were identified *in vitro*. Glycopyrronium (1 and 10 μM) was poorly metabolised by human liver microsomes (only 20% after 150 min), while it was more readily metabolised in mouse, rat and minipigs liver microsomes with clearance values of 121, 593 and 346 μL/min/mg protein, respectively. *In vitro* metabolism studies suggest that glycopyrronium undergoes hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative termed 2(RS)-2-cyclopentyl-2-hydroxy-2-phenylacetic acid.

Non-clinical investigations of glycopyrronium excretion have been performed in mice and rats after oral and intravenous administration and in rats after intratracheal administration. After intratracheal and oral administration, glycopyrronium was mainly excreted via faeces. Following intravenous administration, glycopyrronium was found in higher amounts in the urine than in the faeces or bile. It is likely that the majority of orally administered glycopyrronium is not absorbed, which is consistent with the low bioavailability observed in rats and humans after oral administration. This hypothesis is further supported by observations that in rodents, the majority of the radioactivity in faeces was attributed to unchanged drug (> 60% of the detected radioactivity) after oral administration.

Toxicology

Repeat-dose studies with oral administration of glycopyrronium were conducted in mice (0, 30, 100 and 300 mg/kg/day) and rats (0, 40, 120 and 360 mg/kg/day). Mydriasis was noted in all test groups treated with glycopyrronium. Observed histopathological effects were of minimal to mild severity and did not appear to reflect dose-limiting toxicity. These studies revealed clinical signs that included mydriasis, tachycardia, prostration, anorexia and diarrhoea consistent with exaggerated pharmacological effects and, at very high doses compared to approved clinical doses, drug-induced deaths.

Repeat-dose toxicity studies were also conducted in rats (4, 13, and 26 weeks) and dogs (4 and 39 weeks) by inhaled glycopyrronium at doses up to 4 mg/kg/day. The main systemic toxicity findings included mydriasis, changes caused by reduced gland secretion, increase in water consumption, and decrease in food consumption, weight loss and increase in heart rate. These can be attributed to the antimuscarinic effect of glycopyrrolate or secondary effects thereof. In addition, in the rat, irritation of the nasal cavities and larynx, lens opacity (cataract) and epithelial hypertrophy at the bronchiolo-alveolar junction were noted, possibly resulting from muscarinic receptor inhibition. Changes in the respiratory tract were evident at all dose levels in the rat repeat-dose toxicity studies, but not in dogs. This suggests that the innate sensitivity of the upper respiratory tract of rodents may contribute to the observed adverse effects. In dogs, tachycardia was recorded at doses exceeding 0.077 mg/kg/day, most likely due to exaggerated pharmacodynamics effects on the cardiovascular system since glycopyrronium reduces the parasympathetic effect on the heart.

In vitro genotoxicity testing of glycopyrronium including the Ames mutagenicity assay and human (peripheral) lymphocyte chromosome aberration assay has been performed. In addition, the *in vivo* bone marrow micronucleus assay was conducted in rats. No genotoxic effect was observed in any these tests. Glycopyrronium tosylate was negative in an Ames assay, with and without metabolic activation.

The carcinogenic potential of glycopyrronium was tested in a 26-week oral study in CByB6F1-Tg (HRAS)2Jic transgenic mice and a 104-week inhalation study in rats. In a 26-week oral carcinogenicity study, glycopyrronium treatment did not increase the incidence of neoplastic findings in CByB6F1-Tg (HRAS)2Jic transgenic (Tg) and wild-type (WT) mice at the highest doses (75 and 100 mg/kg/day for males and females, resp.; correlated with AUC values for males: 33.1 and 75.6 ng.h/mL for Tg or WT; females: 24.7 and 15.3 ng.h/mL for Tg or WT). In a 2-year carcinogenicity study, the neoplastic incidence rate including but not limited to endometrial stromal polyps and the combination of endometrial stromal polyps plus endometrial stromal sarcoma monitored in Wistar rats treated at dose of 0.06, 0.17 and 0.45 mg/kg glycopyrronium per day did not exceed the spontaneous incidence rate observed in the control animals (twice air or once vehicle); at Week 52, the mean plasma AUC_{0-24} values were 8.2, 22.2 and 36.5 ng.h/mL in the low, mid and high-dose group, respectively.

Fertility and early embryonic development as well as pre- and postnatal development, including maternal function, were investigated in rats after subcutaneous application of glycopyrronium. Embryo-foetal development after inhalation of glycopyrronium has been studied in rats and rabbits. Glycopyrronium has also been administered IV to pregnant rabbits, PO to female rats and injected IM in rats and rabbits in order to study developmental toxicity.

Glycopyrronium was administered subcutaneously to male and non-pregnant female Wistar rats, at doses of up to 1.5 mg/kg/day of glycopyrronium. No effects on male fertility parameters (including sperm counts and sperm motility) were noted, despite plasma exposure levels (AUC) being up to 895-fold higher than observed clinically at therapeutic doses. In females, decreases in the number of corpora lutea and implantation sites were observed for rats receiving glycopyrronium at 1.5 mg/kg/day. No effects on fertility and reproductive performance in male and female rats were observed at a subcutaneous dose of 0.63 mg/kg/day of glycopyrronium. However, impairment of fertility, i.e., decreased implantation sites and live foetuses, was observed in Wistar rats at a subcutaneous dose of 1.88 mg/kg/day of glycopyrronium.

Embryo-foetal development was assessed in pregnant rats receiving glycopyrronium via inhalation during gestation days 6 to 17 and in pregnant rabbits inhaling glycopyrronium during gestation days 7 through 19. In both rats and rabbits, no effects on embryo-foetal development were observed.

Glycopyrronium was administered orally to pregnant rats during organogenesis at doses exceeding the maximum recommended human dose (MRHD) by up to 113 times. No increased incidence of gross external or visceral effects was noted. In rabbits, intravenous administration (about 7.8 times the MRHD) did not have any adverse effects on embryo-foetal development. Reproduction studies were conducted to investigate the teratogenic effects of orally administered glycopyrronium in rats (65 mg/kg/day; 320 times MRHD) and of intramuscular injection of glycopyrronium in rabbits (0.5 mg/kg/day; 5 times MRHD). No teratogenic effects to the foetus were observed, although a dose related decrease in the rate of conception was observed in rats. Pre- and postnatal development was not affected when glycopyrronium was subcutaneously administered to pregnant rats.

No adverse effects of glycopyrronium on the immune organs were observed in standard toxicology studies. In rats, the immune function was assessed in a 4-week inhalation toxicity study with glycopyrronium dosed at 0.08, 0.49 and 3.39 mg/kg/day. There were also no changes in leukocyte distribution or on the primary immune response to sheep erythrocytes.

In order to estimate the risk for phototoxicity, the absorption of light of wavelengths between 200 nm and 700 nm by a 0.05% glycopyrronium solution was analysed. There was no significant light absorption measured in the range of natural sunlight (280 – 700 nm). This suggests there is no significant risk for direct phototoxicity when glycopyrronium is topically applied.

No juvenile toxicity studies can be retrieved to support the safety of glycopyrronium in the intended patient population, however, there are two randomised, placebo-controlled studies that investigated the efficacy and safety of glycopyrronium in children for 24 weeks. In a multicentre, open-label study, the safety and efficacy of oral glycopyrrolate solution 1 mg/5 mL for 24 weeks were evaluated in paediatric patients (n = 137) with chronic moderate-to-severe drooling associated with cerebral palsy and other neurologic conditions. Most patients (n = 122; 89%) had at least one treatment-emergent adverse event (TEAE), 47% of which were deemed related to oral glycopyrrolate solution, with most being mild-to-moderate in intensity. In another randomised Phase III evaluation of the efficacy and safety of a novel glycopyrrolate, 38 patients aged 3–23 years with severe drooling were randomised to glycopyrrolate (n = 20) conditions. All 20 patients treated with glycopyrrolate oral solution and 15 of 18 (83.3%) who received placebo had at least one TEAE, including 15 (75%) and seven (39%), respectively, who had TEAEs considered by the investigator to be related to treatment. Four patients (20%) in the glycopyrrolate oral solution group, but none in the placebo group, had at least one severe TEAE. The most common adverse reactions were dry mouth, vomiting, constipation, and nasal congestion. One open-label study described the use of glycopyrrolate in the control of drooling in children and young adults with cerebral palsy and related neurodevelopmental disabilities over a longer period (n=38; follow-up 8 months-4 years) without providing sufficient details. In another open-label trial, glycopyrrolate was used by 24 children and young adults (n=22; duration 5 weeks to 28 moths) using a questionnaire on the effects of the drug on severity and frequency of drooling and to report any side-effects, but important details are missing from this publication regarding exposure.

Ecotoxicity/Environmental Risk Assessment (ERA)

An Environmental Risk Assessment (ERA) has been provided. The MAH has provided a log n-octanol/water partition coefficient (log K_{ow}) for glycopyrronium of -0.99 to -1.4, this is below the action limit for persistent, bioaccumulative, toxic (PBT) substance screening. The Predicted Environmental Concentration$_{SURFACEWATER}$ ($PEC_{SURFACEWATER}$) has been calculated using a dose of 3 mg and a population of 70,800 children aged 3 to 17 years who experience significant sialorrhoea. The $PEC_{SURFACEWATER}$ is 0.01585 ng/L, which is below the action limit of 0.01 µg/L.

The results of the ERA show that there is no risk of increased environmental exposure with the use of these products.

Clinical Evaluation

About the condition sialorrhoea

Sialorrhoea (drooling or excessive salivation) is an unintentional loss of saliva from th**e** mouth. This condition is normal in infants up to 18 months while sialorrhoea after the age of four is generally considered to be pathological. Sialorrhoea can be caused by excess production of saliva or more commonly, decreased clearance of saliva. The prevalence of drooling in patients with neurological conditions is high.

Drooling can significantly affect a sufferer's quality of life, with physical effects such as perioral chapping, dehydration, interference with feeding, and secondary bacterial infection, and psychological effects including embarrassment, lowered self-esteem, and social isolation.

A multidisciplinary team is often involved in the management of this condition, and a combination of treatment choices are used. These may include non-invasive treatments such as oral motor therapy, practical aids, speech therapy and pharmacological treatment, and invasive treatments such as surgery and radiotherapy.

Clinical overview and clinical summaries
The pharmacological, pharmacokinetic, efficacy and safety properties of glycopyrronium bromide in the proposed indication are well known. A clinical overview and clinical summary of these aspects based on a literature review is, thus, appropriate. The clinical overview submitted is satisfactory and the literature search methodology is acceptable. This variation is supported by a bridging pharmacokinetic study and an observational study using data from the Optimum Patient Care Research Database (OPCRD).

A clinical summary is also provided.

Pharmacokinetics
Pharmacokinetic study
In support of the applications, the MAH submitted the following pharmacokinetic study comparing their 2 mg tablets against a suitable product, Cuvposa oral solution 1 mg/5mL, to establish the bridge to the literature. This study is summarised below:

Study
An open-label, balanced, randomised, single dose, two-treatment, two-sequence, four-period, fully replicate cross over, oral bioequivalence study comparing the test product Glycopyrronium Bromide 2 mg Tablets versus the reference product Cuvposa oral solution 1 mg/5 mL in healthy, adult, human subjects under fasted conditions.

After an overnight fast of 10 hours, subjects were administered one tablet of the test product (1 x 2 mg tablet) or 10 mL of the reference product (equivalent to 2 mg glycopyrronium bromide). 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 is presented below:

Table 1: Least Square means, Geometric Least Square Means, Ratio, 90% confidence intervals, Power and Intra-subject Variability for the Log transformed C_{max} and AUC_{0-t} for glycopyrronium

Parameters (units)	Least Square Means		Geometric Least Square Means		Ratio (%) (T Vs R)	90% Confidence Intervals (%)	Intra Subject CV (%)	Power (T Vs R) (%)
	T	R	T	R				
Ln (C_{max}) (pg/mL)	6.48152612	6.33031525	652.9667	561.3335	116.32	107.94 - 125.36	37.02	99.94
Ln (AUC_{0-t}) (hr *pg/mL)	8.19089348	8.06711693	3607.9444	3187.8977	113.18	105.42 - 121.50	35.02	99.98

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. This relied on the 'replicate design' of the study, where within-subject variability of C_{max} led to a widening of the C_{max} acceptance range. Results show that AUC falls within the acceptance range 80.00-125.00%, and Cmax falls within the widened acceptance range 78.68% - 127.08%. The pharmacokinetic results showed that the test products can be considered similar to the reference products. A bridge to the supporting literature has been established.

The MAH requested a 'biowaiver of additional strength' for the 1 mg tablet. In support of biowaiver, the MAH provided satisfactory data to support linear pharmacokinetics. As the additional strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 2 mg product strength can be extrapolated to the other strength.

The pharmacokinetic results showed that the test products can be considered similar to the reference products. A bridge to the supporting literature has been established.

The MAH cited the relevant data from the literature to support the pharmacokinetics of glycopyrronium, summarised as follows in the approved SmPC:

'Absorption
Glycopyrronium bromide is poorly absorbed from the gastrointestinal tract. Oral glycopyrronium bromide has low oral bioavailability; a mean of approximately 3% is found in plasma.

Mean absolute oral bioavailability of glycopyrronium comparing a single 50 µg/kg oral dose and a single 5 µg/kg i.v. dose was low at approximately 3% (range 1.3–13.3%) in children aged 7–14 years undergoing intraocular surgery (n = 6) due to the medicinal product's low lipid solubility. Data from sparse PK sampling in children suggests dose proportional PK.

Therapeutic doses of oral glycopyrronium bromide produce low plasma concentrations (Cmax 0.318 ± 0.190 ng/ml) lasting up to 12 hours.

Food effect data indicate that the mean C_{max} under fed high-fat meal conditions is ~75% lower than the C_{max} observed under fasting conditions.

Distribution
The bioavailability of oral glycopyrronium in children is between that of adults under fed and fasted conditions. Co-administration with food results in a marked decrease in systemic glycopyrronium exposure.

In adults, distribution of glycopyrronium was rapid following a single 6 µg/kg i.v. dose; distribution half-life was 2.2 ± 1.3 minutes. Following administration of ^{3}H-labelled glycopyrronium >90% of the radiolabel disappeared from plasma in 5 minutes, and almost 100% within 30 minutes, reflecting rapid distribution. Analyses of population pharmacokinetic data from healthy adults and children with cerebral palsy-associated chronic moderate to severe drooling who received glycopyrronium (route of administration

and dosages unspecified) did not demonstrate linear pharmacokinetics of the medicinal product.

The volume of distribution, 0.64 ± 0.29 L/kg in adults is similar to that of total body water. Volume of distribution is somewhat higher in the paediatric population in the range 1.31 to 1.83 L/kg.

The PK of glycopyrronium has been shown to be essentially independent of age in children 0.19-14 years administered a 5 µg/kg i.v. single-dose. In most paediatric subjects, plasma glycopyrronium vs. time plots are reported to show a triexponential curve; adults generally show a biexponential curve. Modest changes in volume of distribution (Vss) and clearance (Cl) have been observed in children between 1 and 3 years of age, leading to a statistically significantly shorter elimination half-life (t½) than that observed in younger (<1 year of age; p = 0.037) or older (>3 years of age; p = 0.042) groups.

In a study in healthy adults, a 2000 µg single dose of glycopyrronium bromide resulted in an AUC of 2.39 µg.h/L (fasted). An $AUC_{0\text{-}6\ h}$ of 8.64 µg.h/L was observed after 6 µg/kg i.v. glycopyrronium.

Based upon theoretical physicochemical considerations, the quaternary ammonium compound glycopyrronium would be expected to have low central bioavailability. No glycopyrronium was detected in the CSF of anaesthetised surgical patients or patients undergoing caesarean section following a 6-8 µg/kg i.v. dose. In the paediatric population 5 µg/kg i.v. glycopyrronium has low central bioavailability, except in the case where the blood brain barrier has been compromised (e.g. a shunt infection).

The primary route of elimination of glycopyrronium is via renal excretion, mainly as unchanged medicinal product. Approximately 65% of an i.v. dose is renally excreted within the first 24 hours. A small proportion (~5%) is eliminated in the bile.

The elimination half-life of glycopyrronium appears to be dependent on route of administration: 0.83 ± 0.27 hours after i.v. administration, 75 minutes after i.m. administration and ~2.5-4 hour after oral (solution) administration, though this was highly variable. The latter two half-lives, and especially that for oral administration, are longer than for i.v. administration probably reflecting the complex absorption and distribution of glycopyrronium by each route. It is possible that prolonged absorption after oral administration translates into elimination being faster than absorption (flip-flop kinetics).

The total body clearance of the medicinal product following an i.v. dose is relatively high at between 0.54 ± 0.14 L/h/kg and 1.14 ± 0.31 L/h/kg. Since this exceeds the glomerular filtration rate and more than 50% of the dose is excreted unchanged in the urine, it is probable that the renal elimination of glycopyrronium involves both glomerular filtration and proximal tubular basal secretion.

A mean increase in total systemic exposure (AUC_{last}) of up to 1.4 fold was seen in adult subjects with mild and moderate renal impairment (GFR ≥30 mL/min/1.73m2) and up to 2.2 fold in subjects with severe renal impairment or end stage renal disease (estimated GFR <30 mL/min/1.73m2). A 30% dose reduction is required for patients with mild to moderate renal impairment. Glycopyrronium is contraindicated in patients with severe renal impairment.

Baseline characteristics (age, weight, gender and race) do not affect the pharmacokinetics of glycopyrronium.

Glycopyrronium bromide penetrates the blood-brain barrier poorly. Glycopyrronium bromide crosses the placenta to a limited extent; it is not known whether it is distributed into milk.

Biotransformation
In adult patients who underwent surgery for cholelithiasis and were given a single IV dose of tritiated glycopyrronium bromide, approximately 85% of total radioactivity was excreted in urine and < 5% was present in T-tube drainage of bile. In both urine and bile, > 80% of the radioactivity corresponded to unchanged drug. These data suggest a small proportion of i.v. glycopyrronium bromide is excreted as one or more metabolites.

Elimination
A study using intravenous 3H-glycopyrronium bromide in humans showed the disappearance of more than 90% from serum in 5 minutes and almost 100% in 30 minutes. Urinary radioactivity was highest in the first 3 hours and 85% was excreted in the urine within 48 h. 80% of the radioactivity in bile and urine was unchanged glycopyrronium bromide. Following oral administration to mice, 7.6% was excreted in the urine and ~79% in the faeces.

Impaired hepatic function is not expected to affect the pharmacokinetics of glycopyrronium since the majority of the medicinal product is eliminated through the kidneys.

Co-administration with food results in a marked decrease in systemic glycopyrronium exposure (see section 4.2.).

Different formulations of glycopyrronium differ in bioavailability and should not be regarded as interchangeable (see section 4.2).'

Pharmacodynamics
The MAH cited the relevant data from the literature to support the pharmacodynamic effects of glycopyrronium, summarised as follows in the approved SmPC:

'Glycopyrronium bromide is a synthetic muscarinic anticholinergic agent that binds competitively to the muscarinic acetylcholine receptor. Like other anticholinergic (antimuscarinic) agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions.'

Clinical efficacy
The MAH cited the relevant data from the literature to support the efficacy of glycopyrronium in the proposed indication. The pharmacokinetic study comparing the MAH's product against Cuvposa acted as a 'bridge to the literature'. Efficacy data are summarised as follows in the approved SmPC:

'Placebo-controlled efficacy data for sialorrhoea in children includes patients with a treatment duration of 8 weeks. There is no placebo or comparator-controlled data beyond 8 weeks.

Zeller et al 2012 evaluated the efficacy of glycopyrronium bromide oral solution (1 mg/5mL) in managing problem drooling associated with cerebral palsy and other neurological conditions.

Thirty-eight patients aged 3-23 years weighing at least 12.2 kg with severe drooling (clothing damp 5-7 days/week) were randomized to 8 weeks treatment with glycopyrronium (n = 20), 20-100 µg/kg (not exceeding 3 mg in total), or matching placebo (n = 18) tds. The first 4 weeks were an individual titration period in fixed steps depending on response, followed by 4-weeks maintenance treatment.

The primary efficacy endpoint was responder rate, defined as percentage showing ≥3-point improvement on the modified Teacher's Drooling Scale (mTDS). The primary analysis population was revised to only comprise patients with an age of 3 -16 years with 19 patients in the glycopyrrolate oral solution group and 17 in the placebo group. Responder rate was defined as at least a 3-point improvement in modified Teacher's Drooling Scale (mTDS).

Drooling Scale (mTDS).

Treatment	**At least a 3-point improvement in mTDS**	**Mean improvement in mTDS**
Glycopyrronium	14 of 19 patients (73.7%)	3.94 points (SD: 1.95; 95%; CI: 2.97–4.91)
Placebo	3 of 17 patients (17.6%)	0.71 points (SD: 2.14; 95% CI: –0.43–1.84)
p value	p = 0.0011	p <0.0001

84% of physicians and 100% of parents/caregivers regarded glycopyrrolate as worthwhile compared with 41% and 56%, respectively, for placebo (p≤0.014). Most frequently reported treatment-emergent adverse events (glycopyrrolate vs placebo) were dry mouth, constipation, vomiting and nasal congestion.

In a separate study by Zeller et al (2012), the safety and efficacy of glycopyrronium were studied in an open-labelled study without a control group over a 24-week period in children aged 3-18 years At the week 24 exit visit, 52.3% (95% CI 43.7–60.9) of Clinical

In a separate study by Zeller et al (2012), the safety and efficacy of glycopyrronium were studied in an open-labelled study without a control group over a 24-week period in children aged 3-18 years At the week 24 exit visit, 52.3% (95% CI 43.7–60.9) of patients (n=130) had an at least three point decrease in mTDS from baseline and were classified as responders to treatment with oral glycopyrrolate solution with 83.5% of parents/caregivers and 85.8% of investigators rating oral glycopyrrolate solution as worthwhile. The adverse event profile was consistent with that seen with anticholinergics (see section 4.4 and 4.8).'

Clinical safety

The MAH cited the relevant data from the literature to support the safety of glycopyrronium in the proposed indication. The pharmacokinetic study comparing the MAH's product against Cuvposa acted as a 'bridge to the literature'. Evidence from the literature was provided to support Sections 4.3, 4.4, 4.5, and 4.8 of the approved SmPC as follows:

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- *Glaucoma*
- *Urinary retention*
- *Severe renal impairment (eGFR <30 ml/min/1.73m^2, including those with end stage renal disease requiring dialysis*
- *History of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis and myasthenia gravis*
- *Pregnancy and breast-feeding*
- *Concomitant treatment with (see section 4.5);*
    - *potassium chloride solid oral dose*
    - *anticholinergics*

Special warnings and precautions for use

<u>Anticholinergic effects</u>

Anticholinergic effects such as urinary retention, constipation and overheating due to inhibition of sweating may be dose dependent and difficult to assess in a disabled child. Monitoring by physicians and caregivers is required with adherence to the management instructions below:

Management of important anticholinergic side effects:

The carer should stop treatment and seek advice from the prescriber in the event of:

- *constipation*
- *urinary retention*
- *pneumonia*
- *allergic reaction*
- *pyrexia*
- *very hot weather*
- *changes in behaviour*

After evaluation, the prescriber should decide if treatment should be discontinued or if it should be continued at a lower dose.

<u>Lack of long-term safety data</u>

Published safety data are not available beyond 24 weeks treatment duration. Given the limited long-term safety data available and the uncertainties around the potential risk for carcinogenicity, total treatment duration should be kept as short as possible. If continuous treatment is needed (e.g. in a palliative setting) or the treatment is repeated intermittently (e.g. in the non palliative setting treating chronic disease) benefits and risks should be carefully considered on a case by case basis and treatment should be closely monitored.

<u>Mild to moderate sialorrhoea</u>

Due to the low likelihood of benefit and the known adverse effect profile, Glycopyrronium bromide tablets should not be given to children with mild to moderate sialorrhoea.

Cardiac disorders
Glycopyrronium should be used with caution in patients with acute myocardial infarction, hypertension, coronary artery disease, cardiac arrhythmias and conditions characterised by tachycardia (including thyrotoxicosis, cardiac insufficiency, cardiac surgery) due to the potential increase in heart rate, blood pressure and rhythm disorders produced by its administration. The carer should be advised to measure the pulse rate if the child seems unwell and report very fast or very slow heart rate.

Gastro-intestinal disorders
Antimuscarinics such as glycopyrronium should be used with caution in patients with gastro-oesophageal reflux disease, pre-existing constipation and diarrhoea.

Dental
Since reduced salivation can increase the risk of oral cavities and periodontal diseases, it is important that patients receive adequate daily dental hygiene and regular dental health checks.

Respiratory
Glycopyrronium can cause thickening of secretions, which may increase the risk of respiratory infection and pneumonia. Glycopyrronium should be discontinued if pneumonia is present.

CNS adverse events
Increased central nervous system effects have been reported in clinical trials including: irritability; drowsiness; restlessness; overactivity; short attention span; frustration; mood changes; temper outbursts or explosive behaviour; excessive sensitivity; seriousness or sadness; frequent crying episodes; fearfulness. Behavioural changes should be monitored.

As a consequence of its quaternary charge glycopyrronium has limited ability to penetrate the blood brain barrier, although the extent of penetration is unknown. Caution should be exercised in children with compromised blood brain barrier e.g. Intraventicular shunt, brain tumour, encephalitis.

Children below the age of 3 years
Glycopyrronium Bromide is not recommended for use in children below the age of 3 years since there is very limited data on the efficacy and safety of glycopyrronium in this age group.

Growth and development
The effects of glycopyrronium on the reproductive system have not been investigated.

Whilst clinical studies do not report any short or long-term effect of glycopyrronium on neurodevelopment or growth, no studies have been conducted to specifically address these issues.

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take this medicine. This is due to the presence of sorbitol (E420) in this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per maximum dose, i.e. essentially is 'sodium free '.

Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

Paediatric population
There are limited data available relating to interactions with other medicinal products in the paediatric age group.

The following medicinal product interaction information is relevant to glycopyrronium.
Contraindications of concomitant use
Concomitant use of the following medicinal products is contraindicated (see section 4.3):

Potassium chloride solid oral dose: glycopyrronium may potentiate the risk of upper gastrointestinal injury associated with oral solid formulations of potassium chloride due to increased gastrointestinal transit time creating a high localized concentration of potassium ions. An association with upper GI bleeding and small bowel ulceration, stenosis, perforation, and obstruction has been observed.

Anticholinergics: concomitant use of anticholinergics may increase the risk of anticholinergic side effects. Anticholinergics may delay the gastrointestinal absorption of other anticholinergics administered orally and also increase the risk of anticholinergic side effects.

Concomitant use to be considered with caution
Concomitant use of the following medicinal products should be considered with caution:

Antispasmodics: glycopyrronium may antagonize the pharmacologic effects of gastrointestinal prokinetic active substances such as domperidone and metoclopramide.

Topiramate: glycopyrronium may potentiate the effects of oligohidrosis and hyperthermia associated with the use of topiramate, particularly in pediatric patients.

Sedating antihistamines: may have additive anticholinergic effects. A reduction in anticholinergic and/or antihistamine dosage may be necessary.

Neuroleptics/antipsychotics: the effects of active substances such as phenothiazines, clozapine and haloperidol may be potentiated. A reduction in anticholinergic and/or neuroleptic/antipsychotic dose may be necessary.

Skeletal muscle relaxants: Use of anticholinergics after administration of botulinum toxin may potentiate systemic anticholinergic effects.

Tricyclic antidepressants and MAOIs: may have additive anticholinergic effects. A reduction in anticholinergic and/or tricyclic antidepressants and MAOIs dosage may be necessary.

Opioids: active substances such as pethidine and codeine may result in additive central nervous system and gastrointestinal adverse effects, and increase the risk of severe constipation or paralytic ileus and CNS depression. If concomitant use cannot be avoided, patients should be monitored for potentially excessive or prolonged CNS depression and constipation.

Corticosteroids: Steroid-induced glaucoma may develop with topical, inhaled, oral or intravenous, steroid administration. Concomitant use may result in increased intraocular pressure via an open- or a closed-angle mechanism.

Other
Medicinal products with anticholinergic properties (e.g. antihistamines, antidepressants) may cause cumulative parasympatholytic effects including dry mouth, urinary retention, constipation and confusion, and an increased risk of anticholinergic intoxication syndrome.

Undesirable effects
Summary of the safety profile
Adverse reactions are common with glycopyrronium due to its known pharmacodynamic anticholinergic effects. The efficacy of the medicinal product should be balanced against the adverse reactions and the dose monitored regularly and adjusted as necessary. The most common anticholinergic adverse reactions in the placebo-controlled studies (see section 5.1) related to the gastrointestinal system and were dry mouth, constipation, diarrhoea and vomiting, all of which occurred at a rate of ≥15%. The safety profile is further characterised by other symptoms, related to the anticholinergic effects at a rate of ≥15%, including urinary retention, flushing and nasal congestion.

Adverse reactions are more common with higher doses and prolonged use.

Tabulated summary of adverse reactions
Adverse reactions reported in the literature for trials using glycopyrronium for sialorrhoea in the paediatric population (including 2 placebo controlled trials, an uncontrolled safety study using glycopyrronium for a 6 month period, and 3 supportive studies with adverse event data in the target population) are listed by MedDRA system organ class (Table below). Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

Adverse reaction	***Frequency***
Infections and infestations	
Upper respiratory tract infection	*Common*
Pneumonia	*Common*
Urinary tract infection	*Common*
Psychiatric disorders	
Irritability	*Very common*
Agitation	*Common*
Drowsiness	*Common*
Restlessness	*Not known*
Overactivity	*Not known*

Short attention span	*Not known*
Frustration	*Not known*
Mood variable	*Not known*
Temper tantrum	*Not known*
Intermittent explosive disorder	*Not known*
Sensitivity, shyness, and social withdrawal disorder specific to childhood or adolescence	*Not known*
Feeling sad	*Not known*
Crying	*Not known*
Fear	*Not known*
Nervous system disorders	
Headache	*Uncommon*
Insomnia	*Not known*
Eye disorders	
Mydriasis	*Uncommon*
Nystagmus	*Uncommon*
Angle-closure glaucoma	*Not known*
Photophobia	*Not known*
Dry eyes	*Not known*
Cardiac disorders	
Flushing	*Very common*
Transient bradycardia	*Not known*
Respiratory, thoracic and mediastinal disorders	
Nasal congestion	*Very common*
Epistaxis	*Common*
Reduced bronchial secretions	*Very common*
Sinusitis	*Not known*
Gastrointestinal disorders	
Dry mouth	*Very common*
Constipation	*Very common*
Diarrhoea	*Very common*
Vomiting	*Very common*
Halitosis	*Uncommon*
Oesophageal candidiasis	*Uncommon*
Gastrointestinal motility disorder	*Uncommon*
Pseudo-obstruction	*Uncommon*
Nausea	*Not known*

Skin and subcutaneous tissue disorders	
Rash	*Common*
Dryness of the skin	*Not known*
Inhibition of sweating	*Not known*
Renal and urinary disorders	
Urinary retention	*Very common*
Urinary urgency	*Not known*
General disorders and administration site conditions	
Pyrexia	*Common*
Dehydration	*Uncommon*
Thirst in hot weather	*Uncommon*
Angioedema	*Not known*
Allergic reaction	*Not known*

Description of selected adverse reactions
Urinary retention
Urinary retention is a known adverse reaction associated with anticholinergic medicinal products (15%). Glycopyrronium treatment should be withdrawn until the urinary retention resolves.

Pneumonia
Pneumonia is a known adverse reaction associated with anticholinergic medicinal products (7.9%). Glycopyrronium treatment should be withdrawn until the pneumonia resolves.

Constipation
Constipation is a known adverse reaction associated with anticholinergic medicinal products (30%). Glycopyrronium treatment should be withdrawn until the constipation resolves.

Central Nervous System
Although glycopyrronium has limited ability to cross the blood brain barrier, increased central nervous system effects have been reported in clinical trials (23%). Such effects should be discussed with the carer during treatment reviews and a dose reduction considered.

Cardiac disorders
Glycopyrronium is known to have an effect on heart rate and blood pressure at doses used during anaesthesia although clinical trials in children with chronic drooling have not shown this effect. An effect on the cardiovascular system should be considered when assessing tolerability.

Haematology and chemistry
A decrease of >10% from the normal reference range at baseline for absolute neutrophil (11.2%) and red blood cell (11.1%) count, and increases >10% from the normal reference range at baseline for monocyte (16.7%) and absolute monocyte (11.2%) counts has been seen. Decreases >10% from the normal reference range at baseline were observed for carbon dioxide (15.1%), bicarbonate (13.3%), and creatinine (10.7%) concentrations.

Risk Management Plan (RMP)

The MAH has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The authorisations are conditional on the basis that, in addition to routine pharmacovigilance and risk minimisation measures, the following additional risks and safety measures are proposed

Educational materials in the form of:

- The carer and patient information pack containing
  - PIL
  - Reminder Card for the patient's carer
- Physician educational material containing
  - SmPC
  - Healthcare professionals (HCP) checklist

The authorisations are conditional upon the following conditions being met according to the resolution date shown:

Prior to the marketing of Assicco 1mg and 2 mg Tablets/Glycopyrronium Bromide 1 mg and 2 mg tablets, the MAH must agree with MHRA the content, format and distribution of Educational Materials for Healthcare Professionals and for Carers of the Patient, as detailed in Annex 6 of the Risk Management Plan.

The Reminder Card for the Patient's Carer, shall include the following key messages:

- Information on the administration of glycopyrronium bromide, including a dose administration table to be completed by the prescribing doctor.
- Management and minimisation of side effects including:
  - Increased Heart Rate
  - Constipation
  - Urinary Retention
  - Pneumonia
  - Overheating in patients with fever or in hot environments
  - Dental disease due to reduced salivation
  - CNS effects and change in behaviour
  - Allergic Reaction
- Directions regarding further communication with the doctor, including when to seek immediate advice; telling the doctor if the patient has taken or will take other medicines; the frequency of review regarding glycopyrronium medication.

The Checklist for Healthcare Professionals, shall include:

- Information on the administration of glycopyrronium bromide
- A checklist for assessment of anticholinergic effects
- Important information to be brought to the attention of patient's carer including: The Patient Information Leaflet, the Reminder Card for the Patient's Carer, dose directions, recommended observations of the patient, recognition of side effects, avoidance of exposure to hot environments, when to contact the doctor.

Target Resolution Date: 18/03/2026

This is acceptable.

User Consultation

The MAH provided suitable justification for non-submission of an updated user test.

Conclusion
The proposed changes are acceptable.

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature.

Extensive clinical experience with glycopyrronium bromide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflet (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Grant

Date: 18 March 2021