Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Glycopyrronium Bromide 1mg Tablets
Glycopyrronium Bromide 2mg Tablets

(Glycopyrronium bromide)

PL 15764/0156 - 0157

Strandhaven Limited (trading as Somex Pharma)

LAY SUMMARY

Glycopyrronium Bromide 1mg Tablets
Glycopyrronium Bromide 2mg Tablets
(glycopyrronium bromide)

This is a summary of the Public Assessment Report (PAR) for Glycopyrronium Bromide 1mg and 2mg 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 a medicine that has a well-established use. This means that the use of the active substance in this medicine 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 patients suffering from long term neurological disorders which have occurred in childhood, in patients aged 3 years and older.

How do Glycopyrronium Bromide Tablets work?
Glycopyrronium bromide (the active substance in Glycopyrronium Bromide Tablets) belongs to a group of medicines called 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.

Sialorrhoea (drooling or excessive salivation) is a common symptom of many diseases of the nerves and muscles. It is mostly caused by poor control of muscles in the face. Acute sialorrhoea may be associated with inflammation, dental infections or infections of the mouth. Glycopyrronium Bromide Tablets act on the salivary glands to reduce production of saliva.

How are Glycopyrronium Bromide Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (via the mouth).

This medicine should be given at least **one hour before or two hours after a meal**. If the patient's specific needs determine that co-administration with food is required, it is important to give Glycopyrronium Bromide Tablets at consistent times in relation to food intake. Do not give this medicine with high fat foods. If the patient has trouble with swallowing, an oral solution may be more appropriate.

Children and adolescents aged 3 years and older and adults who have suffered from neurological disorders from childhood
The initial dose will be calculated based on the weight of the patient. Dose increases will be decided by the patient's doctor, using the table below as a guide, and will depend on both the effect of Glycopyrronium Bromide Tablets and any side effects the patient is experiencing,

which is why several dose levels appear on the table below. Section 4 of the package leaflet includes possible side effects related to the use of Glycopyrronium Bromide Tablets. These should be discussed with the patient's doctor, including those for dose increases and decreases, and at any other time should the patient's caregiver or patient be concerned.

Glycopyrronium Bromide Tablets are recommended for short-term intermittent use.
The patient should be monitored at regular intervals (at least every 3 months) to check that Glycopyrronium Bromide Tablets is still the right treatment for them.

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

The tablet product may not be suitable for certain dose levels. Dose adjustments should be conducted in discussion with the caregiver to assess both effectiveness of this medicine and any undesirable effects experienced until an acceptable maintenance dose is achieved.

Children under the age of 3 MUST NOT take Glycopyrronium Bromide Tablets.

The patient's doctor will tell their caregiver how long to take the treatment for. The patient should NOT stop earlier than they are told, even if they feel better.

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.

This medicine can only be obtained with a prescription.

The patient should always be given the medicine exactly as their doctor/pharmacist has advised. The patient/carer should check with their 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 Tablets is a safe and efficacious treatment for excessive production of saliva (sialorrhoea) in patients suffering from long term neurological disorders which have occurred in childhood, in patients 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 this medicine, 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 patients suffering from long term neurological disorders which have occurred in childhood, in patients 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. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of 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 SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

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

Other information about Glycopyrronium Bromide Tablets
Marketing Authorisations for Glycopyrronium Bromide Tablets were granted in the UK on 20 April 2016.

Following approval the Marketing Authorisations underwent a change of ownership procedure on 11 March 2021 from the company Kinedexe UK Ltd (PL 44710/00017 - 0018) to Strandhaven Limited (PL 15764/0156 - 0157).

The full PAR for Glycopyrronium Bromide Tablets follows this summary.

This summary was last updated in June 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 Glycopyrronium Bromide Tablets (PL 44710/0017 - 0018) could be approved.

The products were initially approved on 20 April 2016, 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 17 December 2020, the products were approved for a new indication of symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older (refer to Annex 1 at the end of this report).

Glycopyrronium is a quaternary ammonium antimuscarinic with peripheral effects similar to atropine.

Antimuscarinics are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves. They also inhibit the action of acetylcholine where smooth muscle lacks cholinergic innervation.

Salivation is primarily mediated by parasympathetic innervation of the salivary glands. Glycopyrronium competitively inhibits cholinergic muscarinic receptors in salivary glands and other peripheral tissues, thus indirectly reducing the rate of salivation. Glycopyrronium has little effect on cholinergic stimuli at nicotinic acetylcholine receptors, on structures innervated by postganglionic cholinergic neurons, and on smooth muscles that respond to acetylcholine but have no cholinergic innervation.

Peripheral antimuscarinic effects that are produced as the dose increases are: decreased production of secretions from the salivary, bronchial and sweat glands; dilatation of the pupils (mydriasis) and paralysis of accommodation (cyclopegia); increased heart rate; inhibition of micturition and reduction in gastrointestinal tone; inhibition of gastric acid secretion.

The initial applications were submitted under Article 10a of Directive 2001/83/EC, as amended (regulation 54 of The Human Medicines Regulation 2012, 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.

Following approval the Marketing Authorisations underwent a change of ownership procedure on 11 March 2021 from the marketing authorisation holder (MAH) Kinedexe UK Ltd (PL 44710/00017 - 0018) to the MAH Strandhaven Limited (PL 15764/0156 - 0157).

Summary of key post approval changes:

1. To extend the shelf life of Glycopyrronium Bromide 1mg and 2mg Tablets from 2 years to 3 years. Consequentially the section 6.3 of the SmPC has been updated (PL 44710/0017-0007 & PL 44710/0018-0006 granted 26/04/2018).
2. To introduce a change in therapeutic indication for Glycopyrronium Bromide 1mg and 2mg Tablets, following a 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. The new indication is 'symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older. As a consequence, the PIL and sections 2, section 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated (PL 44710/0017-0010 & PL 44710/0018-0009 granted 17/12/2020).
   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 1 at the end of this PAR for further details.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 1mg or 2mg of glycopyrronium bromide.

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

Both strengths (1mg and 2mg tablets) of the finished product are packed into white high-density polyethylene (HDPE bottles) with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 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.

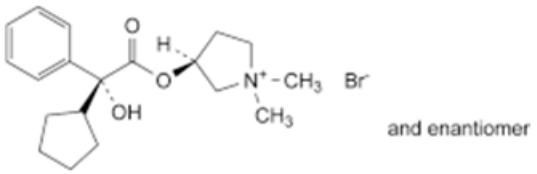
II.2 ACTIVE SUBSTANCE

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:



Molecular Weight: 398.3 g/mol

Appearance: White or almost white, crystalline powder.

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

Glycopyrronium bromide is the subject of a European Pharmacopoeia monograph.

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

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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

With the exception of anhydrous lactose, none of the excipients used contain material of animal or human origin. The supplier of anhydrous lactose has confirmed that the milk used

in the production of anhydrous lactose 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 product
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 2 years for the unopened bottle with no special storage conditions, is acceptable. The in-use shelf life is 3 months after first opening.

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 (regulation 54 of The Human Medicines Regulation 2012, as amended), as 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.

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

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 44710/0017-0010 & PL 44710/0018-0009 (granted 17/12/2020) for a change in indication. Please refer to Annex 1 at the back of this report for the assessment of the MAH's current approved ERA.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use.

The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical pharmacology data, efficacy data or safety data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of glycopyrronium bromide.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable**.**

IV. 2 Pharmacokinetics
Overview
Glycopyrronium bromide is 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide. Glycopyrrolate exists in four distinct stereo isometric forms due to the presence of two chiral centres in the glycopyrrolate molecule. One of the two enantiomeric pairs of diastereomers of glycopyrrolate is (*R*,*R*)-glycopyrrolate and (*S*,*S*)-glycopyrrolate, and the other enantiomeric pair is (*R*,*S*)-glycopyrrolate and (*S*,*R*)-glycopyrrolate.

Glycopyrrolate occurs as a white, odourless crystalline powder. It is soluble in water and alcohol and practically insoluble in chloroform and ether. It is completely ionised at physiological pH values.

Absorption
Oral glycopyrrolate has low oral bioavailability; a median of 3.3% is found in plasma. Oral glycopyrrolate produces low plasma concentrations (C_{max} 190-440 pg/mL) lasting up to 12 hours.

In an open study with eight healthy male volunteers, after a single IV bolus of glycopyrrolate (5µg/kg) the C_{max} was 198 ± 137 (ng/mL) and AUC was 5.16 ± 0.97 (ng.h/mL).

The pharmacokinetics of glycopyrrolate after a single intramuscular dose demonstrate a very rapid absorption rate with C_{max} of 6.3 (1.5) ng/mL and T_{max} 10 (3.8) minutes. The respective AUC value from 0 to 8 hours was 5.61 (1.27) ng.h/mL.

Table 1: Summary of pharmacokinetic parameters for glycopyrrolate after oral administration of 2 mg as glycopyrrolate liquid under fasted and fed conditions and as Robinul (glycopyrrolate) tablet under fasted conditions (Glycopyrrolate, MR, CDER, USFDA Review, 2010)

Parameter*	Glycopyrrolate liquid 2 mg (1 mg/ 5 mL) fasted	Robinul® tablet 2 mg (2 × 1 mg) fasted	Glycopyrrolate liquid 2 mg (1 mg/ 5 mL) fed
C_{max} (ng/mL)	0.318±0.189(37)	0.406±0.197(37)	0.084±0.081(36)
T_{max} (h)	2.53(37) (0.50-6.00)	3.00(37) (1.50-6.00)	2.50(36) (1.00-6.08)
$AUC_{(0-t)}$ (h × ng/mL)	1.74±1.07(37)	2.34±1.03(37)	0.38±0.14(36)
$AUC_{(0-\infty)}$ (h × ng/mL)	1.81±1.09(37)	2.45±1.15(36)	0.46±0.13(35)
λz (/h)	0.2626±0.0965	0.2528±0.1025(36)	0.2325±0.0551(35)
$t_{1/2}$ (h)	3.02±1.20(37)	3.31±1.57(37)	3.21±1.05(35)
*Arithmetic mean±standard deviation (N) except for T_{max} for which the median (N)(range) is reported			

The food effect data indicate the mean C_{max} under fed (high fat meal) conditions is about 74% lower than the C_{max} observed under fasting conditions. Similarly the mean AUC of treatment given under fed conditions was 3 to 4 times lower than those observed for the treatment given under fasted conditions. These data indicate that a high fat meal reduces the oral bioavailability of glycopyrrolate.

Distribution
In an open study with eight healthy male volunteers, after a single IV bolus of glycopyrrolate (5µg/kg) the volume of distribution at steady state was 0.37 ± 0.26 L/kg. After IV injection of 0.006mg/kg, the mean distribution phase half-life was 2.22 ± 1.26 minutes.

Metabolism
It is reported that only 20% of bioavailable drug is metabolised and 80% is excreted unchanged in urine and bile in man.

In a study, the metabolism of scopolamine and glycopyrrolate was studied in 11 healthy subjects having undergone Caesarean section. Glycopyrrolate concentrations increased only slightly between 1 and 3 hours after the drug injection. Thus, it was suggested that β-glucuronide or sulphate conjugation plays only a minor part in the metabolism of glycopyrrolate.

In adult patients who underwent surgery for cholelithiasis and were given a single IV dose of titrated glycopyrrolate, 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 that a small proportion of IV glycopyrrolate is excreted as one or more metabolites.

Excretion
In a study glycopyrrolate was labelled in one methyl group with tritium and its fate was studied in six patients with T-tube drainage by determining serum levels as well as the biliary and urinary excretion of radioactivity after i.v. injection. More than 90 % of the radioactivity had disappeared from serum in 5 min and after 30 min almost no radioactivity could be found.

The highest radioactivity in bile was found in samples taken 30 or 60 minutes after the injection. However, measurable radioactivity was found in most cases after 48 hours (h). The first urine samples (0-3 h) showed the greatest radioactivity, and in 48 h, 85% of the total radioactivity was excreted into the urine. Paper chromatography showed that in both, in bile and in urine, over 80 % of the radioactivity corresponded to unchanged glycopyrrolate. The

excretion of appreciable amounts of glycopyrrolate into the bile suggests that the spasmolysis achieved with glycopyrrolate could be based partly on a local action on the bile ducts.

In a study investigating the pharmacokinetics of glycopyrrolate in 11 uraemic patients undergoing cadaveric renal transplantation and in seven ASA I control patients undergoing general surgery, glycopyrrolate 4 μg/kg was given intravenously (i.v.) before induction of anaesthesia. Volume of distribution (V_d) in the elimination phase was similar in both groups, the elimination half-life ($t_{1/2}$) was longer ($P < 0.05$), AUC larger ($P < 0.01$) and plasma clearance (CL) smaller ($P < 0.01$) in the uraemic patients. In 3 h, mean 0.7% (range 0-3) and 50% (21-82) of glycopyrrolate was excreted in the urine in the uraemic and healthy patients, respectively ($P < 0.001$). The 24 h renal excretion was 7% (0-25) in uraemic and 65% (30-99) in control patients ($P < 0.001$). The authors concluded that the elimination of glycopyrrolate was severely impaired in uraemic patients.

Special populations

Elderly

The basic pharmacokinetic properties of glycopyrrolate were evaluated in a study through radio receptor assay in elderly patients (59-79 years). The patients in Group I were premedicated with glycopyrrolate 4 mg orally and those in Group 2 with glycopyrrolate 8μg/kg i.m., group 3 the patients received a combination anaesthesia (thiopentone 3-5 mg/kg, vecuronium 0.1 mg/kg, $N_2O + O_2$, fentanyl 3 μg/kg and neostigmine as an anticurarizing agent in incremental doses up to 1.25 mg) and glycopyrrolate 6 μg/kg was injected i.v. just before the induction of anaesthesia. Based on the plasma levels after a single i.v. injection, 6 pg/kg (n = 6), the distribution phase $t_{1/2}$ (2.22±1.26 SD min) and the elimination phase $t_{1/2}$ (0.83±0.29 h) of glycopyrrolate were short due to the low distribution volume during the elimination phase (0.64±0.29 L/kg) and the respectively high total plasma clearance value (0.54±0.14 L/kg/h). An intramuscular injection, 8 pg/kg (n = 6) was followed by a fast and predictable systemic drug absorption and clinical effects (heart rate increase, dry mouth). In this group, the time to maximum plasma concentration (T_{max}) was 27.48±6.12 min and the C_{max} was 3.47±1.48 pg/L. After oral drug intake of 4 mg (n = 6), an apparently low and variable gastrointestinal absorption was found (T_{max} = 300.0±197.2 min, C_{max} = 0.76±0.35 pg/L), thus indicating that the oral route of drug administration is of no value as a routine premedication. However, the oral glycopyrrolate produced significant antisialogogue effect.

The applicant's formulation (Glycopyrronium Bromide 1mg and 2mg Tablets) is indicated for add-on therapy in the treatment of peptic ulcer and not as premedication. Many studies which also included elderly patients, have shown that oral glycopyrrolate is effective in the treatment of peptic ulcer. Also in the above study, oral glycopyrrolate produced significant antisialogogue effect. Hence, it can be said that oral glycopyrrolate can be prescribed in elderly patients for the treatment of peptic ulcer.

Children

In a study in six children operated on twice over a period of several weeks and receiving a single p.o. (50 μg/kg) and i.v. (5 μg/kg) dose of glycopyrrolate, plasma levels were determined with a radio receptor assay and resulted in the pharmacokinetic parameters displayed in Table 2:

Table 2: Pharmacokinetic parameters glycopyrrolate in children (Rautakorpi P et al, 1998).		
Parameter	Intravenous (5 µg/kg)	Oral (50 µg/kg)
V_{ss} (L/kg)	1.37 (0.75-2.64)	--
Cl (L/kg/h)	1.09 (0.60-1.43)	--
$AUC_{(0-\infty)}$ (µg/L×min)	276.3 (210.2-502.8)	106.6 (38.5-287.7)
$t_{1/2}$ (h)	139 (73-239)	--
T_{max} (min)	--	90 (30-480)
C_{max} (µg/L)	--	0.37 (0.19-0.44)
Bioavailability (%)	--	3.3 (1.3- 13.3)
Data presented as [Median (Range)]		

Overall conclusions on pharmacokinetics
The pharmacokinetics of glycopyrronium bromide are well known and adequately presented in the applicant's dossier. No new pharmacokinetic data were submitted and none were required for an application of this type.

Bioequivalence
No bioequivalence study has been conducted to support these bibliographic applications.

IV.3 Pharmacodynamics

Introduction
Glycopyrrolate inhibits parasympathetic transmission by selective blockade of acetylcholine at muscarinic receptors. It has little effect on cholinergic stimulation at nicotinic receptors at physiological doses, on structures innervated by postganglionic cholinergic neurones and on smooth muscles which respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrioventricular node, exocrine glands and the autonomic ganglia. By this mechanism, glycopyrrolate reduces the volume and acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions.

Primary pharmacodynamics and mechanism of action
Glycopyrrolate inhibits the action of acetylcholine on peripheral acetylcholine (muscarinic M3) receptors on smooth muscle, cardiac muscle, the sino-atrial and atrioventricular nodes, exocrine glands and, to a lesser degree, autonomic ganglia. Thus it diminishes the volume and free acidity of gastric secretion.

Secondary Pharmacodynamics
Glycopyrrolate also, by dint of its inherent pharmacology, exerts a physiological antisialogogue effect. It is also useful in reverting the bradycardic effects of many anaesthetic drugs, as well as possessing a significant antispasmodic effect.

Pharmacodynamic interactions
Glycopyrrolate increased serum levels of digoxin and haloperidol. Glycopyrrolate, alone or in combination with aluminium hydroxide, clearly retards ethambutol absorption. Glycopyrrolate may increase the bioavailability of atenolol.

Overall conclusions on pharmacodynamics
The pharmacodynamics of glycopyrronium bromide are well known and adequately presented in the applicant's clinical overview.

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type. The clinical efficacy of glycopyrronium bromide is well-established. Efficacy is adequately reviewed in the clinical overview.

The applicant has provided an extensive assessment of the up to date published literature on the efficacy of glycopyrronium bromide in the treatment of peptic ulcers by way of reduction in gastric acid secretion secondary to anticholinergic effects. The majority of the literature is fifty years in the public domain and few recent studies have been carried out to repeat the efficacy demonstrated in these original clinical trials. No new efficacy data have been presented.

One study demonstrated a positive therapeutic response in 92% (n=46 of 50) patients with varying gastroenterological complaints who were prescribed glycopyrronium bromide at doses between 3-8mg. The drug was shown to have marked antisecretory and antispasmodic effects and was effective in acute and chronic duodenal ulcers.

One study looked at 39 ambulant patients with uncomplicated peptic ulceration who received glycopyrrolate at doses between 4-8mg daily. All patients became asymptomatic on glycopyrrolate and the ulcer healed in 31 of the 39 patients. A reduction in gastric acidity was observed in 12 of 15 patients studied. Due to the excellent acid inhibition, coupled with minimal suppression of motility, glycopyrrolate was considered by the authors to be a useful anticholinergic agent.

In a placebo controlled study, patients were enrolled to receive either glycopyrrolate or placebo following resolution of the acute phase of chronic duodenal ulcer and were followed up for 18 months. After this period, the incidence of recurrence of duodenal ulceration was 15% in the glycopyrrolate group and 71% in the placebo group, leading the authors to the conclusion that the use of glycopyrrolate in long term ulcer therapy can minimise the recurrence of episodes.

Similarly, in a comparative double-blind efficacy trial in 120 patients with peptic ulcers comparing glycopyrrolate, propantheline bromide and placebo, glycopyrrolate was found to be more effective than propantheline, and both drugs superior to placebo. Symptomatic relief was seen in the glycopyrrolate group after an average 3.5 days, compared to 7.5 days in the propantheline group.

In another study, glycopyrrolate was compared to atropine in the treatment of active or recurrent peptic ulceration as well as other gastrointestinal disorders, in a randomised double-blind trial. Of 16 patients, thirteen in the glycopyrrolate, atropine or both groups responded favourably, with glycopyrrolate producing fewer side effects.

In a single-blind, controlled trial, glycopyrrolate was compared to 1-hyoscyamine in the long term therapy of duodenal ulcer. In this study 106 male patients with duodenal ulcer were enrolled with 91 completing the study. They were randomised to receive, either, glycopyrrolate, 1-hyoscyamine or placebo for one year. After this period, 79% of patients in the glycopyrrolate group experienced fewer and less severe symptoms and used fewer antacids and had radiologically improved parameters. In this study, this compared to 65% improvement in the 1-hyoscyamine group and 72% in the placebo group; this is unlikely to represent clinical significance.

In various non-controlled studies, glycopyrrolate was administered either alone or as combination with other drugs such as phenobarbital for a variety of gastrointestinal disorders. In these studies, good effects were observed with glycopyrrolate use as evidenced by complete remission of symptoms, acceleration of ulcer healing times or reduction in pain symptoms. The authors conclude that glycopyrronium bromide given in maximum tolerated doses might be an effective addition to present inpatient therapy of chronic gastric ulceration. In one of the studies, satisfactory results were observed in 94.9% of patients with significant side effects in only 2.6%.

Overall conclusions on clinical efficacy
The clinical efficacy of glycopyrronium bromide is well established and an adequate review of the clinical literature has been presented by the applicant to confirm the efficacy of the drug in treating peptic ulceration due to muscarinic drive.

IV.5 Clinical safety

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

The applicant has provided an extensive assessment of the published literature on the safety of glycopyrronium bromide in the treatment of peptic ulcers by way of reduction in gastric acid secretion secondary to anticholinergic effects. The majority of the literature is fifty years in the public domain and few recent studies have been carried out to further investigate the safety aspects demonstrated in these original clinical trials. No new safety data have been presented.

Glycopyrrolate has been found to be generally well tolerated and safety aspects have been documented in a number of trials and a list of undesirable effects has been included.

In various trials to evaluate the safety of glycopyrrolate at doses ranging between 1mg and 5mg, the commonest adverse events recorded were dry mouth, dry eyes, hoarseness and occasional blurring of vision. These effects were dose dependent and reduced upon dose reduction. There were no discontinuations due to adverse events, no serious adverse events and no deaths in the studies presented.

Due to the pharmacology of glycopyrrolate, blurred vision, intestinal obstruction or decreased sweating may occur. In patients with fever or in the presence of high ambient temperatures or intense exercise, anticholinergics may produce heat prostration. As an anticholinergic drug, glycopyrrolate should be used with caution in patients with conditions that are exacerbated by such drugs, including autonomic neuropathy, renal disease, ulcerative colitis, hyperthyroidism and cardiac disease.

Glycopyrrolate is contraindicated in patients with glaucoma, gastrointestinal obstruction, paralytic ileus, ulcerative colitis, obstructive uropathy and myasthenia gravis.

The effects of IV glycopyrrolate on maternal and fetal heart rate, heart rate variability and maternal electromechanical intervals and blood pressure were investigated in 20 patients in labour. Fetal heart rate parameters remained constant but maternal heart rate increased with decreases in electromechanical interval associated with tachycardia. Uterine activity increased in all cases. From this is may be concluded that glycopyrronium bromide is not recommended during pregnancy.

It is unknown whether glycopyrrolate or its metabolites are excreted in human milk, hence use during lactation is not advised.

Overall conclusions on clinical safety
The safety of glycopyrronium bromide is well known and adequately presented through the review of the available literature. No new safety issues are identified.

IV.6 Risk Management Plan (RMP)

The RMP has been revised post-authorisation, submitted as part of variation PL 44710/0017-0010 & PL 44710/0018-0009 (granted 17/12/2020) for a change in indication. Please refer to Annex 1 at the back of this report for the assessment of the MAH's current approved RMP.

IV.7 Discussion on the clinical aspects

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

The bibliographic data submitted for these applications does support the claim of well-established use for the sought indication of use in adults as add-on therapy in the treatment of peptic ulcer.

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 (regulation 260(3) of The Human Medicines Regulation 2012, as amended). 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.

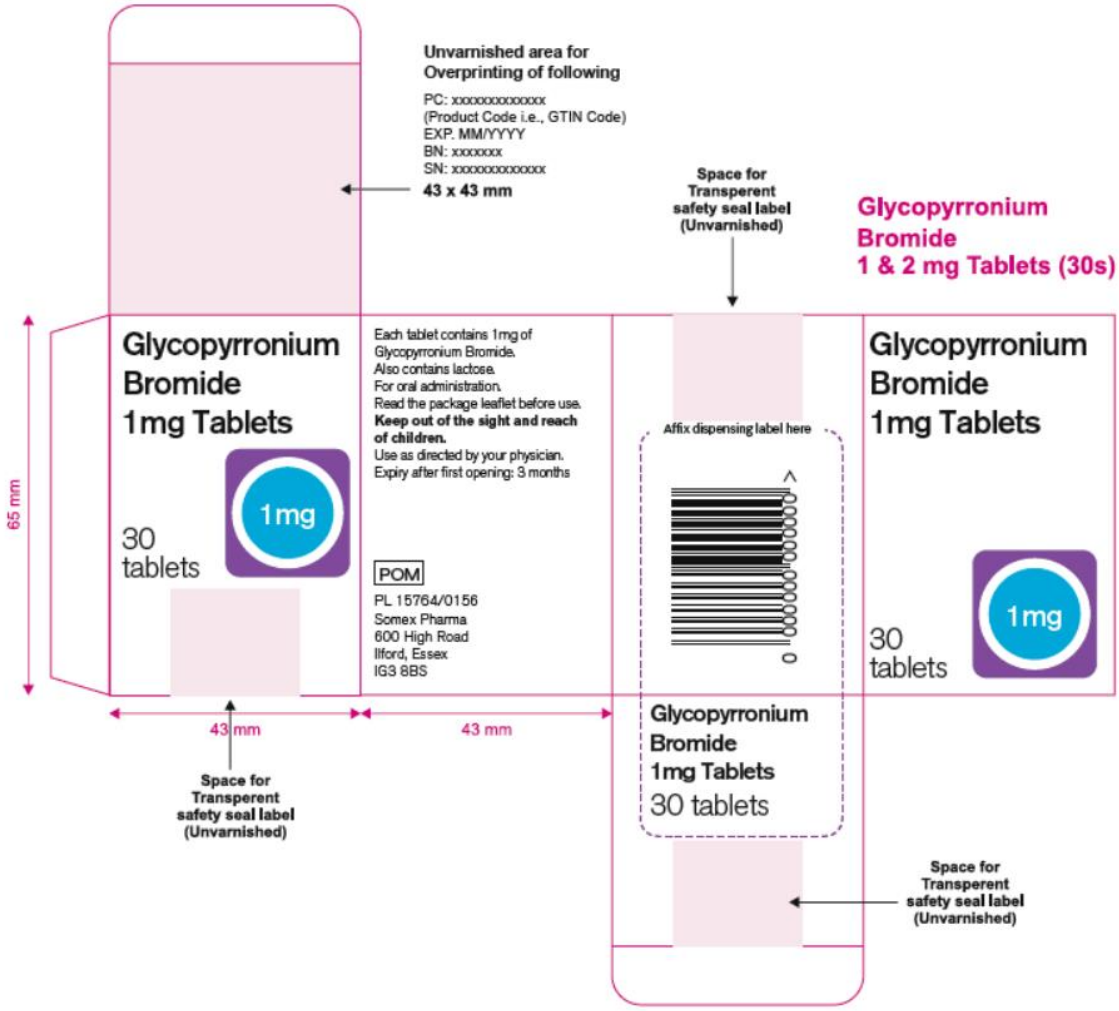
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 (regulation 203(2) of The Human Medicines Regulation 2012, as amended), the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the current approved labels are provided below.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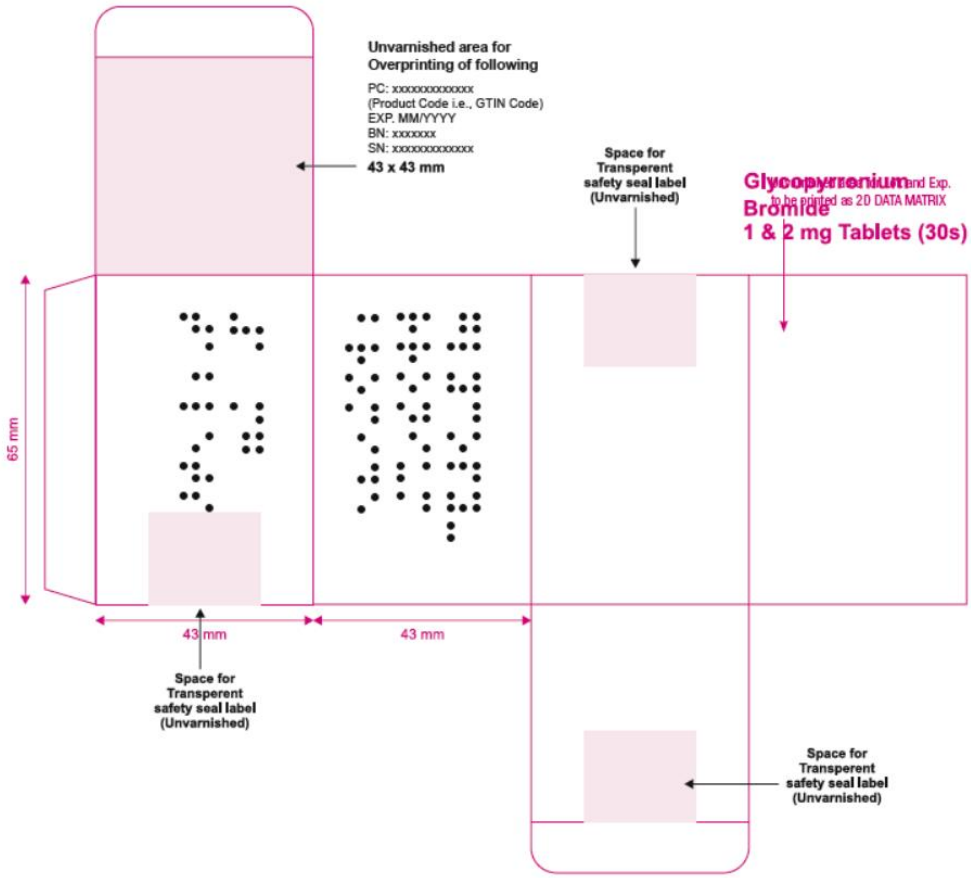
(Product Code i.e., GTIN Code)
EXP. MM/YYYY
BN: xxxxxxx
SN: xxxxxxxxxxxx
43 x 43 mm
Space for
Transperent
safety seal label
(Unvarnished)
Glycopyrronium
Bromide
1 & 2 mg Tablets (30s)
Glycopyrronium
Bromide
1mg Tablets
1mg
30
tablets
65 mm
Each tablet contains 1mg of
Glycopyrronium Bromide.
Also contains lactose.
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach
of children.
Use as directed by your physician.
Expiry after first opening: 3 months
POM
PL 15764/0156
Somex Pharma
600 High Road
Ilford, Essex
IG3 8BS
Affix dispensing label here
Glycopyrronium
Bromide
1mg Tablets
30 tablets
Glycopyrronium
Bromide
1mg Tablets
1mg
30
tablets
43 mm
43 mm
Space for
Transperent
safety seal label
(Unvarnished)
Space for
Transperent
safety seal label
(Unvarnished)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(Product Code i.e., GTIN Code)
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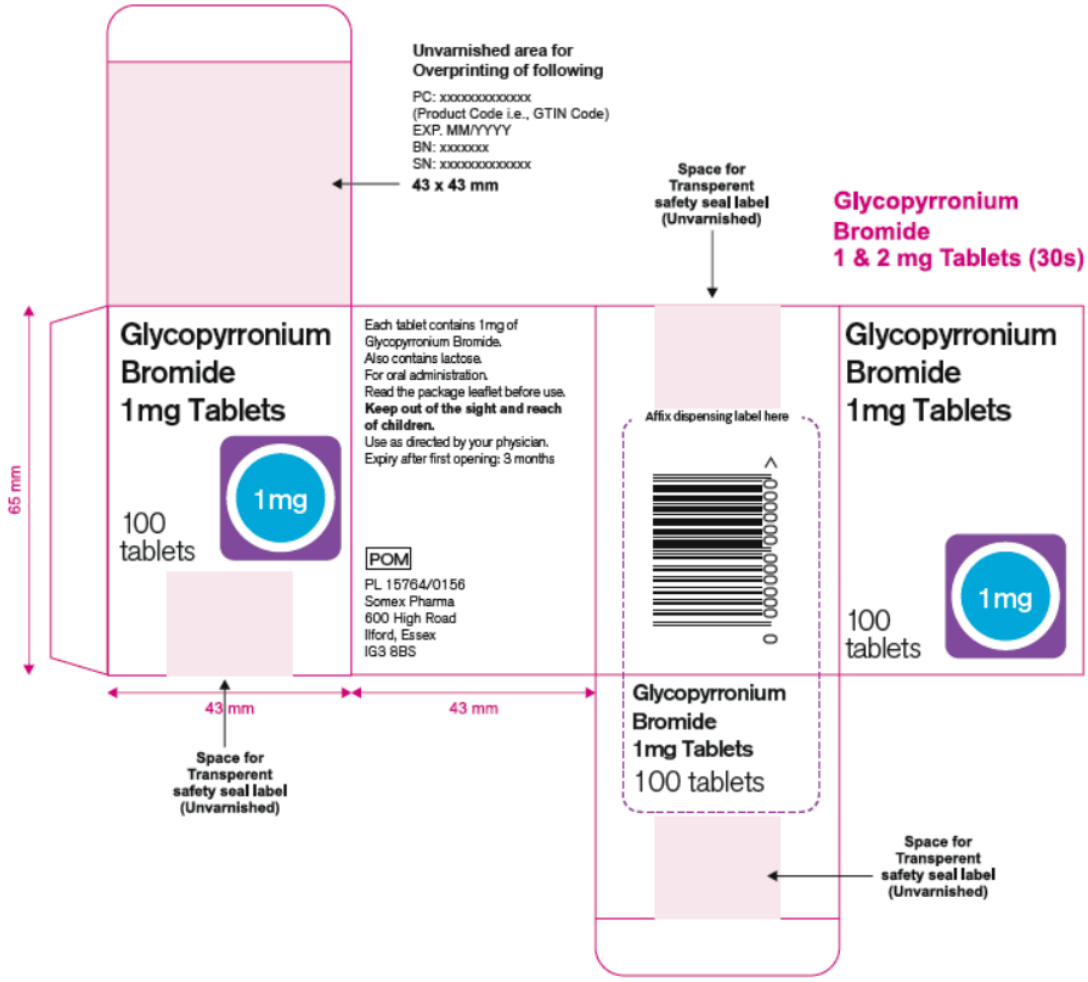
BN: xxxxxx
SN: xxxxxxxxxxxx
43 x 43 mm
Space for
Transperent
safety seal label
(Unvarnished)
Glycopyrronium
Bromide
1 & 2 mg Tablets (30s)
65 mm
43 mm
43 mm
Space for
Transperent
safety seal label
(Unvarnished)
Space for
Transperent
safety seal label
(Unvarnished)


GLYCOPY-
RRONIUM
BROMIDE
#1 MG
TABLETS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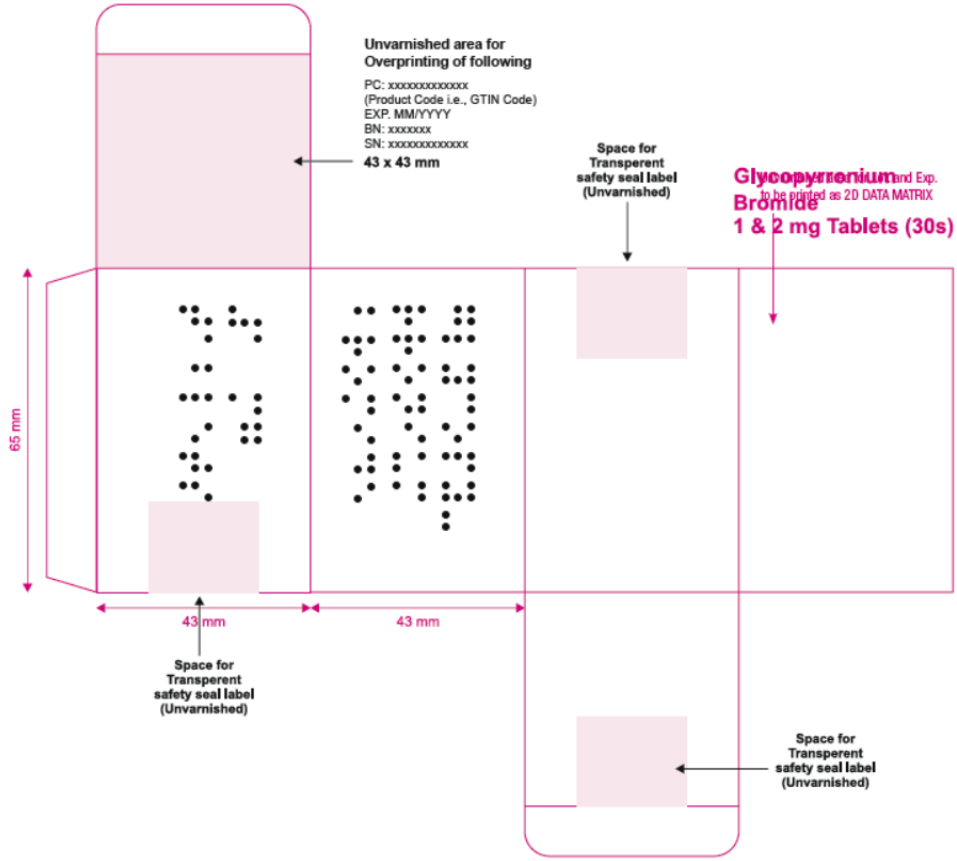
(Product Code i.e., GTIN Code)
EXP. MM/YYYY
BN: xxxxxxx
SN: xxxxxxxxxxxx
43 x 43 mm
Space for
Transperent
safety seal label
(Unvarnished)
Glycopyrronium
Bromide
1 & 2 mg Tablets (30s)
65 mm
Glycopyrronium
Bromide
1mg Tablets
1mg
100
tablets
Each tablet contains 1mg of
Glycopyrronium Bromide.
Also contains lactose.
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach
of children.
Use as directed by your physician.
Expiry after first opening: 3 months
POM
PL 15764/0156
Somex Pharma
600 High Road
Ilford, Essex
IG3 8BS
Affix dispensing label here
Glycopyrronium
Bromide
1mg Tablets
100 tablets
Glycopyrronium
Bromide
1mg Tablets
1mg
100
tablets
43 mm
43 mm
Space for
Transperent
safety seal label
(Unvarnished)
Space for
Transperent
safety seal label
(Unvarnished)

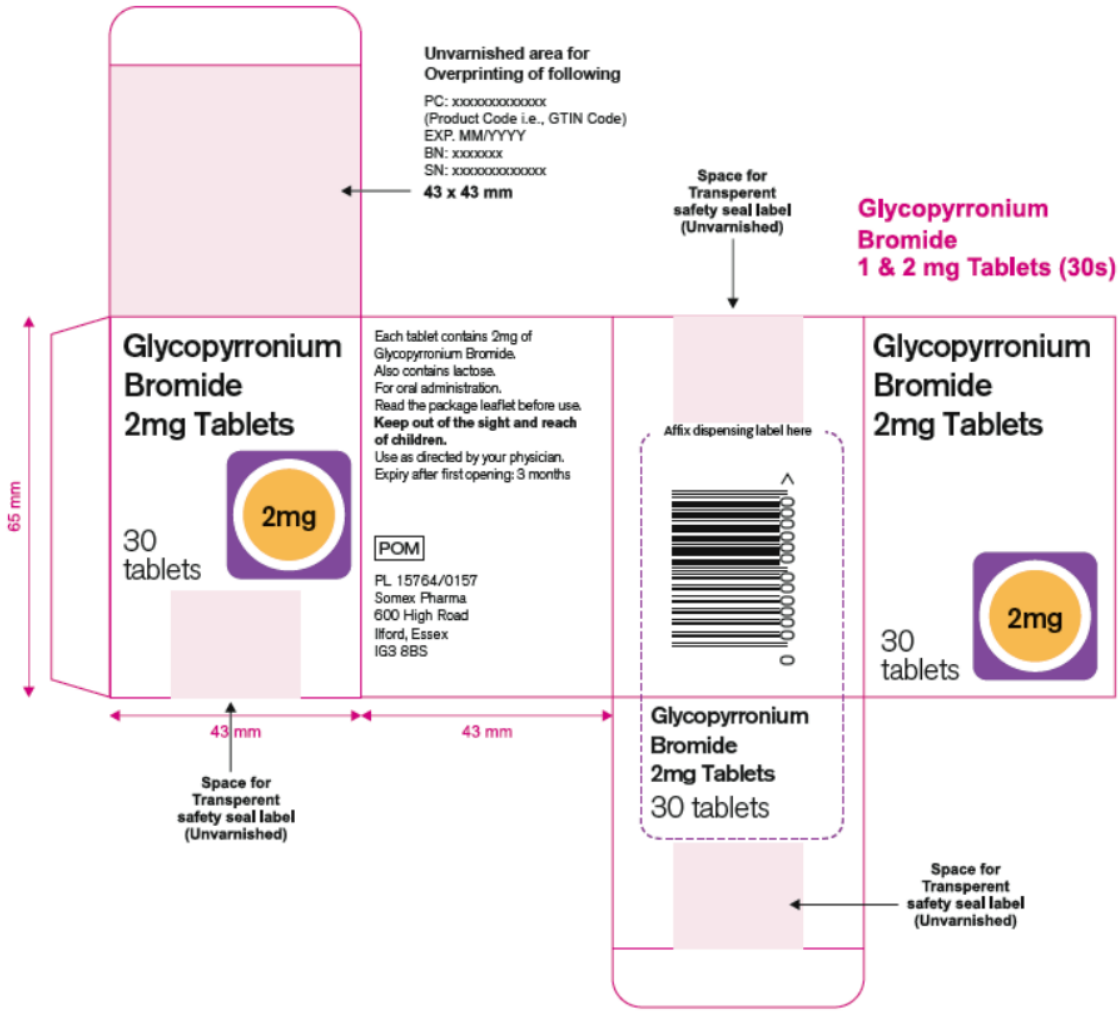


GLYCOPY-
RRONIUM
BROMIDE

#1 MG
TABLETS

Glycopyronium Bromide 1mg & 2mg: 30 Tablets
1mg: 100 Tablets


80 mm
23 mm
Glycopyrronium Bromide 1mg Tablets
100 tablets
1mg
Each tablet contains 1mg of Glycopyrronium Bromide. Also contains lactose. For oral administration. Read the package leaflet before use. Keep out of the sight and reach of children. Use as directed by your physician.
Expiry after first opening: 3 months.
Lot.
Exp.
Unvarnished area for Lot. and Exp. to be printed
MH/DRUGS/PD/182 000000
POM
PL 15764/0156
Somex Pharma, 600 High Road, Ilford, Essex IG3 8BS
PHARMACODE
30cc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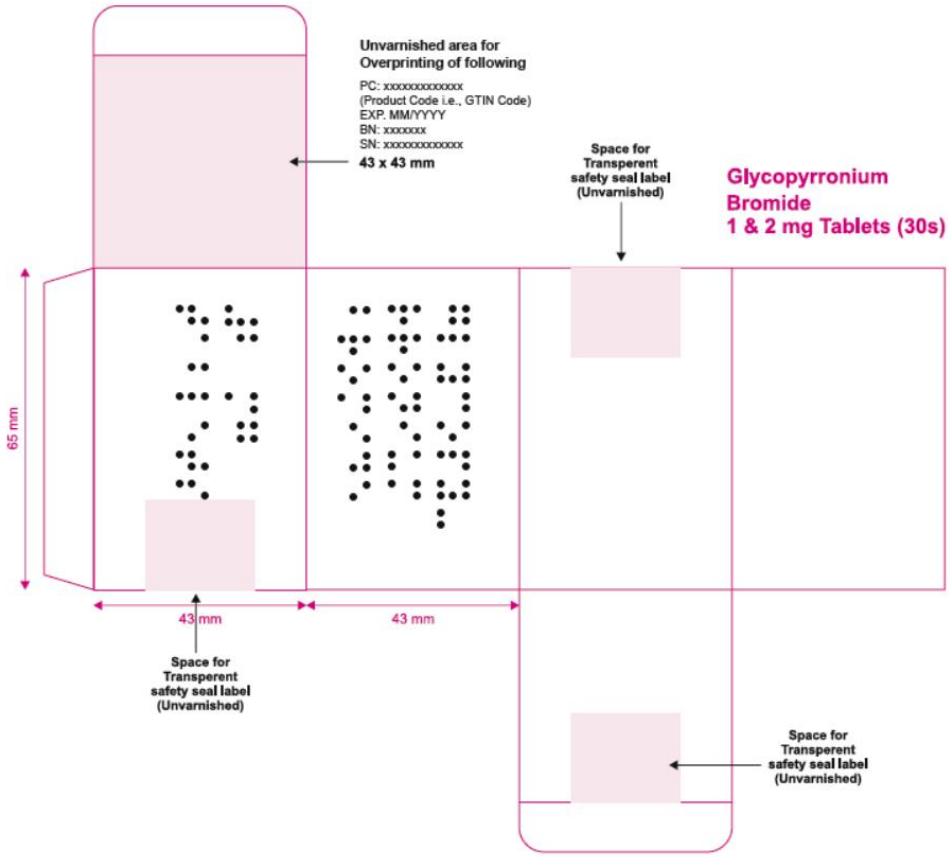
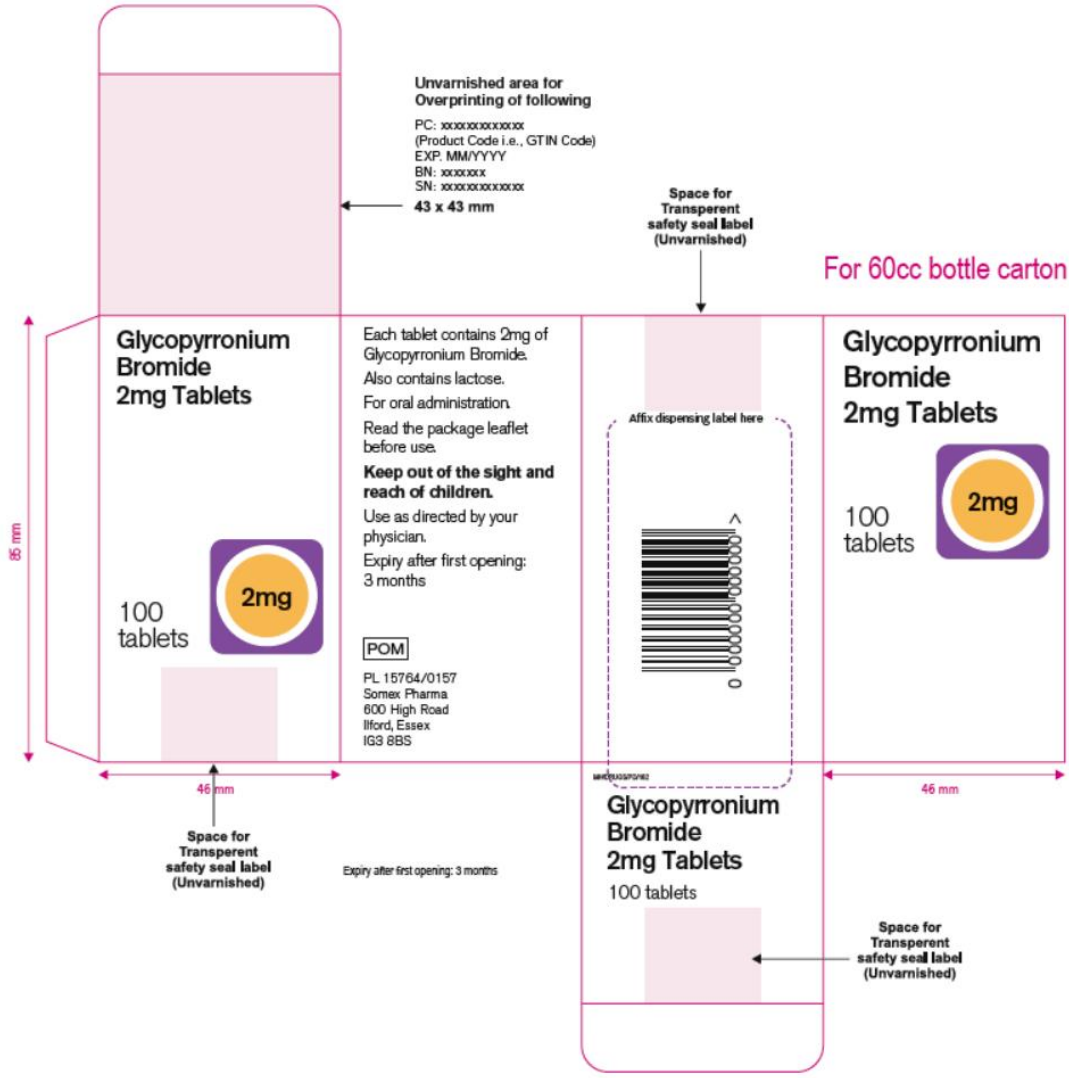
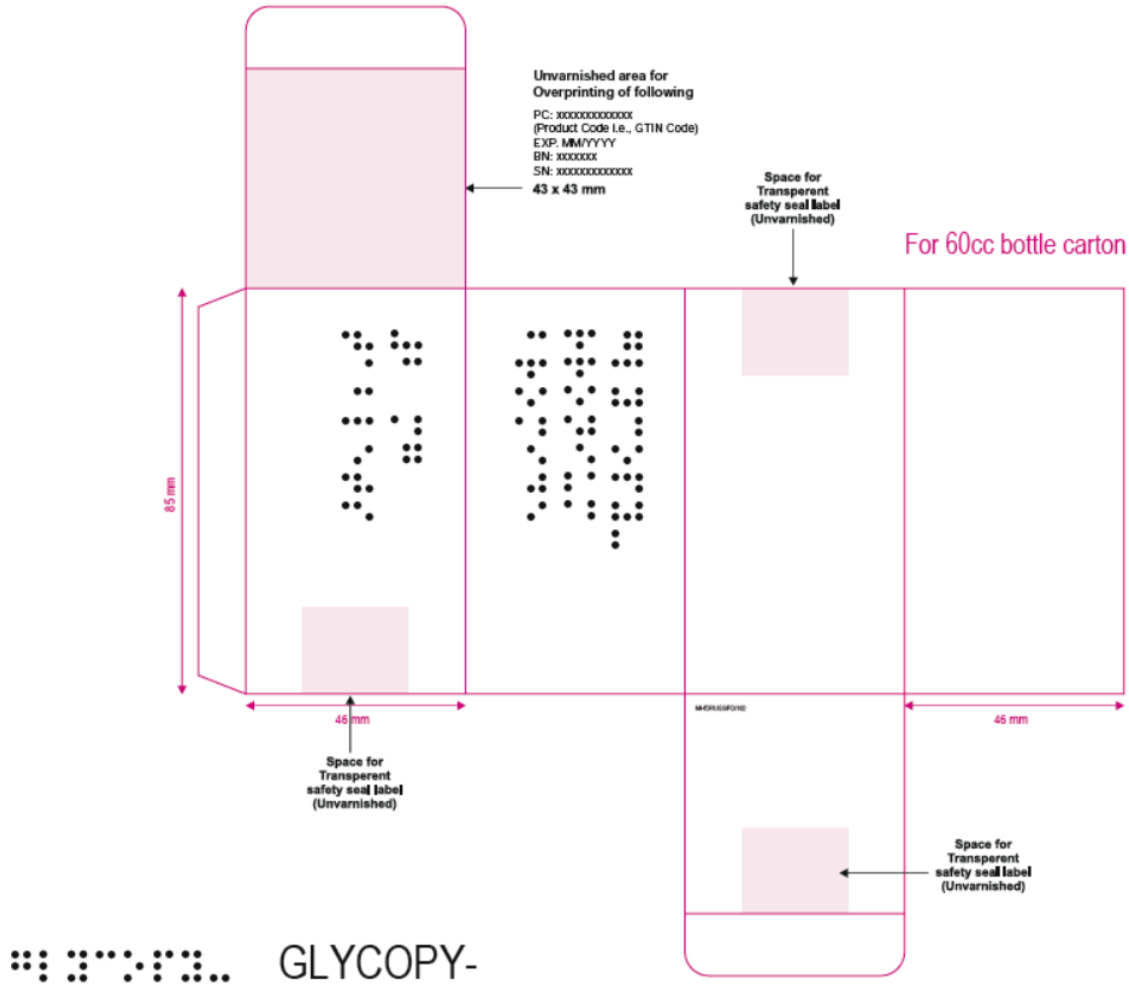
(Product Code i.e., GTIN Code)
EXP. MM/YYYY
BN: xxxxxxx
SN: xxxxxxxxxxxx
43 x 43 mm
Space for Transperent safety seal label (Unvarnished)
Glycopyrronium Bromide 1 & 2 mg Tablets (30s)
65 mm
Glycopyrronium Bromide 2mg Tablets
30 tablets
2mg
Each tablet contains 2mg of Glycopyrronium Bromide. Also contains lactose. For oral administration. Read the package leaflet before use. Keep out of the sight and reach of children. Use as directed by your physician. Expiry after first opening: 3 months
POM
PL 15764/0157
Somex Pharma
600 High Road
Ilford, Essex
IG3 8BS
Affix dispensing label here
Glycopyrronium Bromide 2mg Tablets
30 tablets
43 mm
43 mm
Space for Transperent safety seal label (Unvarnished)
Space for Transperent safety seal label (Unvarnished)

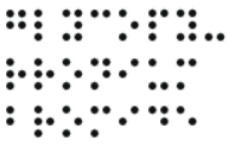


GLYCOPY-
RRONIUM
BROMIDE

#2 MG
TABLETS


Unvarnished area for Overprinting of following
PC: xxxxxxxxxxxx
(Product Code i.e., GTIN Code)
EXP. MM/YYYY
BN: xxxxxxx
SN: xxxxxxxxxxxx
43 x 43 mm
Space for Transperent safety seal label (Unvarnished)
For 60cc bottle carton
Glycopyrronium Bromide 2mg Tablets
100 tablets
2mg
Each tablet contains 2mg of Glycopyrronium Bromide.
Also contains lactose.
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Use as directed by your physician.
Expiry after first opening: 3 months
POM
PL 15764/0157
Somex Pharma
600 High Road
Ilford, Essex
IG3 8BS
Affix dispensing label here
85 mm
46 mm
Space for Transperent safety seal label (Unvarnished)
Expiry after first opening: 3 months
Glycopyrronium Bromide 2mg Tablets
100 tablets
Space for Transperent safety seal label (Unvarnished)





GLYCOPY-
RRONIUM
BROMIDE

#2 MG
TABLETS

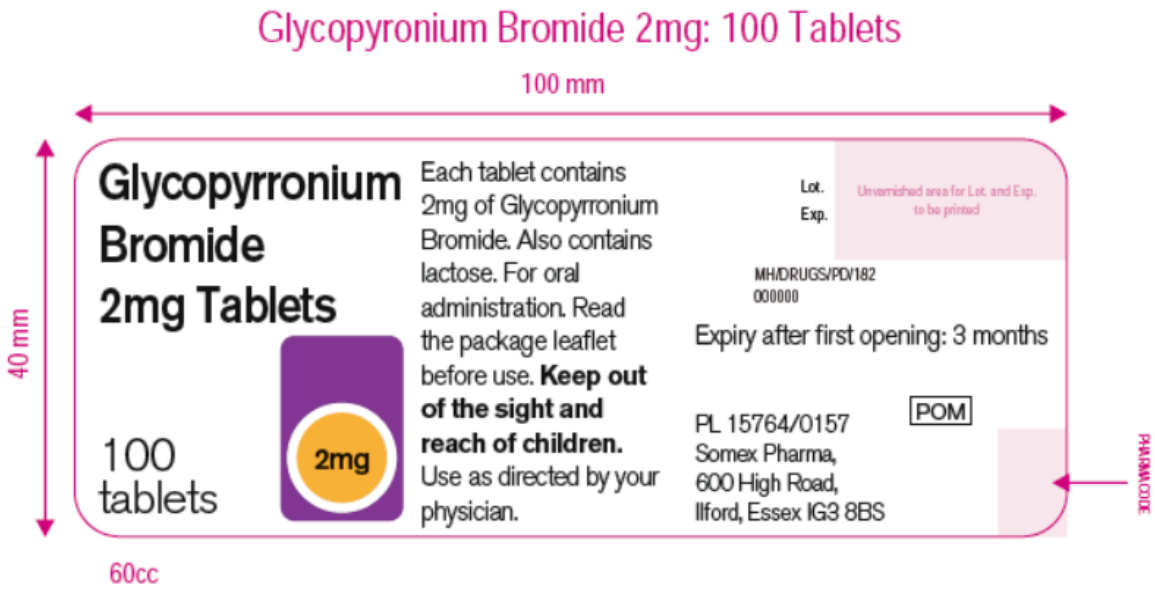

Glycopyronium Bromide 2mg: 100 Tablets
100 mm
40 mm
Glycopyrronium Bromide 2mg Tablets
100 tablets
2mg
Each tablet contains 2mg of Glycopyrronium Bromide. Also contains lactose. For oral administration. Read the package leaflet before use. Keep out of the sight and reach of children. Use as directed by your physician.
Lot.
Exp.
Unvarnished area for Lot. and Exp. to be printed
MH/DRUGS/PD/182 000000
Expiry after first opening: 3 months
POM
PL 15764/0157
Somex Pharma,
600 High Road,
Ilford, Essex IG3 8BS
PHARMACODE
60cc

TABLE OF CONTENT OF THE PAR UPDATE

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

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

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**
Medical Type II (extended)	PL 44710/0017-0010 & PL 44710/0018-To introduce a change in therapeutic indication for Glycopyrronium Bromide 1mg and 2mg Tablets, following a CHM referral which determined that the efficacy data supporting the MA are insufficient to establish the efficacy of Glycopyrronium as add-on therapy in the treatment of peptic ulcer. The new indication is Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older. As a consequence, the PIL and sections 2, section 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated.	SmPC and PIL	17/12/2020	Approved	Y-see Annex 1

Annex 1

References: PL 44710/0017-0010
PL 44710/0018-0009

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

Type of Procedure: National

Submission category: Type II Variation (extended)

Reason
To introduce a change in therapeutic indications for Glycopyrronium Bromide 1mg and 2mg Tablets, following a Commission of Human Medicines (CHM) referral which determined that the efficacy data supporting the MA are insufficient to establish the efficacy of glycopyrronium as add-on therapy in the treatment of peptic ulcer. 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. As a consequence, the PIL and sections 2, 3 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated.

Supporting evidence
The MAH has submitted an updated:

- Variation application form
- Amended SmPC
- SmPC Fragments
- Amended PIL
- pharmaceutical-development-annexure-v
- 2-4-non-clinical overview
- 2-5-clinical overview
- 2-6-non-clinical summary
- 2-7-clinical summary
- A comprehensive bibliography (module 5)

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 1mg and 2mg Tablets were approved in 2016 through the National Procedure under Article 10a of Directive 2001/83/EC, as amended (regulation 54 of The Human Medicines Regulation 2012, as amended), with the indication: '*Use in adults as add-on therapy in the treatment of peptic ulcer*'.

In 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 SmPC.

Advice was sought from the Commission of Human Medicines (CHM) on 24 May 2019, who on the evidence before them had reason to think that on grounds relating to quality, safety and efficacy, they might be unable to advise the grant of this variation. In response to the CHM advice, the MAH provided further data including clinical studies (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 17 December 2020.

Evaluation

Quality Evaluation

PRESENT[9,10]	PROPOSED[9,10]
Therapeutic Indications For use in adults as add-on therapy in the treatment of peptic ulcer.	**Therapeutic Indications** Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adults with chronic neurological disorders. Additional changes have been made to the SmPC, for these changes please refer to the track-change version.

As the new dosage regime requires a dose of 0.5 mg, the results of uniformity of mass of subdivided tablets have been provided for the 1 mg tablets, which have a score-line. The results are well within Ph. Eur acceptance limits.

The MAH initially conducted a bioavailability study between Kinedexe tablets and Robinul Forte tablets (from US) in order to bridge to published studies. However, in these studies, there is no mention of intact Robinul tablets being administered (tablets were either ground into a powder then encapsulated or placed directly in the patient's food or administration of dose was not stated).

Following CHM advice on 24 May 2019, the MAH performed a new bioequivalence study using their 2 mg test product against the reference product Cuvposa oral solution 1 mg/5mL (from US) administered under fasting conditions in healthy, adult, human subjects in a randomised cross over study.

The new study demonstrates that the MAH's 2mg test product is bioequivalent to Cuvposa. Refer to the clinical evaluation below for full details of the bioequivalence study assessment.

Based on the new bioequivalence study, a bridge has been established to literature on Cuvposa oral solution 1 mg/5mL. Both the study and biowaiver data for the 1 mg strength are satisfactory from a pharmaceutical perspective.

As a result, the proposed posology has therefore been revised based on available literature and the MAH's own new bioavailability study to provide a maximum daily dose of 9 mg. With this revised posology, a 2 mg tablet is acceptable.

The product literature has been satisfactorily revised and is acceptable from a quality perspective.

Quality conclusion

From a quality perspective, all outstanding points have been addressed and approval of the variations can be recommended.

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) due to chronic neurological disorders of childhood onset in patients aged 3 years and older.". A summary of the revised non-clinical overview is provided below.

Pharmacology

Anticholinergic drugs are classified either as nicotinic receptor antagonists or as muscarinic receptor antagonists, depending on acetylcholine receptors (nAChRs) specific binding. Nicotinic receptor antagonists act either on the skeletal muscle, on autonomic ganglia and adrenal medulla or on the central nervous system (CNS). Muscarinic receptor antagonists (antimuscarinics) include naturally occurring alkaloids such as atropine and scopolamine, as well as semisynthetic and synthetic alkaloid derivatives. Glycopyrrolate (glycopyrronium) is part of the antimuscarinic group of anticholinergics which find applications as bronchodilators, urinary or gastrointestinal antispasmodics, as well as mydriatic and antiparkinsonian drugs.

Glycopyrronium is a competitive inhibitor of acetylcholine receptors of the M3 subtype that are located on peripheral tissues such as salivary glands. It blocks stimulation of these receptors thereby reducing the extent of salivation.

In anesthetised mongrel dogs, methacholine was used as a stimulating agent and salivary output resulting from each methacholine stimulation was measured before and after IV glycopyrronium. The results indicated that an IV dose of 5 μg/kg produced a marked reduction of salivary secretion.

In human volunteers using a combination of carbamylcholine chloride and adrenaline to stimulate release of saliva, an IV dose of 0.2 mg glycopyrronium was found to be more or similarly effective as 0.4 mg IV atropine in relation to the inhibition of salivary secretion.

In a review article the differences in pharmacological actions of glycopyrronium based on both animal and human data were summarised, as below.

	Atropine	**Glycopyrrolate**
Salivation	Marked inhibition	Marked and prolonged inhibition
Sweat glands	Marked inhibition	Marked and prolonged inhibition
Heart rate	Increase	Minimal Change
Pupil size	Increase	No change
Near point of vision	Increase	No change

In the context of veterinary practice, both atropine sulfate and glycopyrronium are effective when administered to anesthetised dogs and cats in inhibiting sialorrhoea and intestinal peristalsis as well as controlling bradycardia. In these species, glycopyrronium has been shown to be more potent and have more long-lasting effects than atropine.

There was no evidence for glycopyrronium-related CNS effects in general pharmacodynamic studies in anaesthetised dogs, EEG recordings in cats and acute toxicity studies in mice, rats, rabbits, dogs and cats.

One study evaluated the pharmacological and toxicological profile of glycopyrronium in combination with other drugs. In mouse, rat and dog, there was no evidence for any significant pharmacological interaction between glycopyrronium and phenobarbital, meprobamate, tybamate, mephenoxalone or butaperazine. In terms of inhalation therapy, combinations of glycopyrronium with formoterol or indacaterol have been authorised on the basis of showing improved efficacy (compared to monotherapy) in COPD.

Additive effects along with potential toxicity are possible (at least in theory) from co-administration of glycopyrronium with other drugs possessing anticholinergic properties.

Pharmacokinetics

Following IV administration of ^{14}C-glycopyrronium in the mouse, peak radioactivity was found in all organs at 5-10 minutes except brain. Liver, kidney and intestines showed traces of activity at 24 hours. Following oral administration, stomach and small intestine showed the maximum amount of radioactivity and absorption from the gastrointestinal tract was poor. Minimal amounts of glycopyrronium cross the blood-brain barrier. Both animal and human studies show that placental transfer is limited.

Following oral administration ^{14}C-glycopyrronium at 4.83 μCi/mouse, minimal amounts of radioactivity were present in the blood by 0.5 hours and remained detectable for up to 6 hours. Oral absorption was low most likely due to the permanently ionised nature of the drug, 1.9% of the dose being found in the stomach and 6.4% in the small intestine at 3 h post-dose.

After IV administration of ^{14}C-glycopyrronium to mice at 0.966 μCi/mouse, total radiolabelled material was rapidly distributed throughout the body. High levels of radioactivity were observed mainly in the liver (26.1% reducing to 2.1% of dose at 12 h) and also in the kidney, but not in the brain, only a trace of radioactivity being detected at 5 min and none thereafter. After 6 h a total of 13.8% of the dose was present in the small intestine, caecum and large intestine, suggesting a modest extent of biliary excretion. Radioactivity after oral administration was distributed initially to the stomach and at later time-points to the small intestine, caecum and small intestine. No radioactivity was detected in the brain. Liver radioactivity was highest after 6 h at 1.3% of dose.

The levels of ^{14}C-glycopyrronium appearing in cerebrospinal fluid and serum following a single IV dose were determined in anaesthetised mongrel dogs and compared with levels reached in dogs treated with similar doses of ^{3}H-atropine. As early as 10 min after injection, 23% of atropine levels were detected as compared to 2% of glycopyrronium levels. Peak cerebrospinal fluid / serum (CSF/S) concentration ratios for ^{3}H-atropine averaged 0.87, *vs*. a mean ratio of 0.1 for ^{14}C-glycopyrronium within the 4-hour observation period. In pregnant dogs, peak mean fetal serum (FS) levels occurred 10 min after a single intravenous dose of 0.1 mg/kg ^{3}H-atropine administered to the mother and represented 30% of the corresponding maternal serum (MS) concentration. The maximum FS/MS concentration ratio observed within the four-hour post-drug period for ^{3}H-atropine was 1.0 *vs.* 0.04 for ^{14}C-glycopyrronium.

Whole-body autoradiograms showed no radioactivity in the foetus following administration to pregnant animals. After multiple oral administration of radiolabelled glycopyrronium at

3.86 μCi/mouse/day over 1 week, the radioactivity disappeared entirely from organs at 72 h after the last dose, and accumulation was not observed.

Studies of the metabolism of glycopyrronium in animals indicate the major metabolic pathway to be hydroxylation of the cyclopentyl ring and oxidation of the hydroxyl group in the mandelic acid residue. These metabolites have been mainly detected in the liver and kidney.

Following oral administration to mice, 7.6% was excreted in the urine and about 79% in the faeces. When glycopyrronium was administered by the IV and oral routes, 6 metabolites were detected in urine. Major metabolites were considered to be 1,1-dimethyl-3-hydroxypyrrolidinium bromide a-(2- or 3-hydroxy-cyclopentyl) mandelate and 1,1-dimethyl-3-hydroxypyrrolidinium bromide benzoyl formate. 1,1-dimethyl-3-hydroxypyrrolidinium bromide was identified as minor metabolite. Major metabolic pathways of glycopyrronium were assumed to be hydroxylation of cyclopentyl ring and oxidation of hydroxyl group in mandelic acid moiety, then simultaneous removal of cyclopentyl ring.

A study using IV ^{3}H-glycopyrronium in humans showed the disappearance of more than 90% from the 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 hours. Paper chromatography showed 80% of the radioactivity in bile and urine corresponding to unchanged glycopyrronium.

In children aged 7–14 years, the mean absolute bioavailability of oral glycopyrrolnium (50 μg/kg) was reported to be low and variable (median 3.3%; range 1.3 to 13.3%).

Administration of glycopyrronium oral solution 2 mg in fasting healthy adults resulted in mean C_{max} of 0.318 ng/ml after a t_{max} of 2.53 h (mean t_{max} of 3.10 h). The mean $AUC_{0-\infty}$ was 1.81 ng × h/mL. Compared with glycopyrronium tablets, glycopyrronium oral solution had a 23% lower C_{max} and a 28% lower $AUC_{0-\infty}$ suggesting that absorption of glycopyrronium from the tablet formulation is superior to that from the oral solution.

A study using ^{3}H-glycopyrronium in humans showed that 85% of an IV dose was excreted in urine within 48 h and 80% of the activity in bile and urine corresponded to unchanged drug. Hydrolysis with Glusulasc increased glycopyrronium concentrations in urine only by 15% in 3h indicating the minor contribution of glucuronide and sulfate conjugation reactions in the metabolism of glycopyrronium.

In renally-impaired patients, the elimination of IV administered glycopyrronium is severely impaired. Compared to control patients, a significantly smaller plasma clearance, longer elimination half-life and larger AUC were reported. While the 24 h renal excretion was 65% in control patients, it was only 7% in uremic patients.

Toxicology

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

"Non-clinical data, including genotoxicity or carcinogenicity studies have not been performed for glycopyrronium bromide. Limited non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity.

The single-dose toxicity of glycopyrronium has been tested in a range of investigations, although only limited experimental details are available. Upon oral administration, high LD_{50} values of 550 mg/kg in mice and above 1000 mg/kg in rats were reported. In rats at higher doses (1500-2000 mg/kg) signs of toxicity were tremors, clonic and tonic convulsions and laboured breathing were observed prior to death, resulting from respiratory failure.

Chronic oral administration of glycopyrronium at doses of 4, 16 and 64 mg/kg for up to 27 weeks in dogs produced mydriasis, cycloplegia, xerostomia, emesis, occasional lacrimation, injection of sclera and rhinorrhoea.

Extrapolation of safety margins to the paediatric population is not possible, as no exposure data are available from repeated dose toxicology studies and no studies in juvenile animals have been performed with glycopyrronium.

Data on reproductive endpoints for glycopyrronium are very limited. A reduction in corpora lutea was observed in female rats administered glycopyrronium. No effects on fertility were observed in male rats. Reproductive performance in rats given glycopyrronium shows a decrease in the rate of conception and in survival rate at weaning. The significance of the non-clinical findings for humans is not clear, and the lack of human data on the medicinal product leads to glycopyrronium being contraindicated in pregnant women. There are insufficient data in the public domain to adequately assess effects on the reproductive system in young adults, and safety in human pregnancy has not been established."

Elemental impurities risk assessment
A risk assessment on Elemental Impurities (EI) for the drug product was performed in accordance with the Guideline on Elemental Impurities Q3D. None of the categorised EI as defined by Q3D is likely to be present or not prone to reach a level exceeding 30% of the Permitted Daily Exposure (PDE) set for each element. The EI assessment is accepted.

Environmental Risk Assessment (ERA)
A revised ERA has been provided using a maximum dose of 9 mg and using patients with cerebral palsy and Parkinson's disease, resulting in an Fpen of 0.77 ng/L which is below the action limit. Log K_{ow} has been provided as -1.52 from the Robinul injection (now discontinued). Although reference has been made to marketed products the information required to calculate Fpen is not drawn from the data related to them. It is stated that using a figure of 30% patients drooling for Parkinson's disease as opposed to 5% noted in published literature makes allowances for other patients with neurological disease that may have severe drooling. The ERA is accepted.

Statements in the SmPC are supported by adequate literature evidence in the MAH's dossier and the product literature has been satisfactorily revised and is acceptable from a non-clinical perspective.

Non-clinical conclusion
From a non-clinical perspective, all outstanding points have been addressed and approval of the variations can be recommended.

Clinical Evaluation
About the condition sialorrhoea
Sialorrhoea (drooling or excessive salivation) is an unintentional loss of saliva from the mouth. Although normal in infants, drooling usually stops when at 15 – 18 months of age and is considered pathological if present after age 4 years. The most common cause of sialorrhoea

is neuromuscular dysfunction; other causes are hypersecretion and sensory or anatomic dysfunction *e.g.* failure of lip closure or infrequent swallowing. In children with cerebral palsy and other neuromuscular conditions, drooling may be due to hypersalivation and / or oral motor dysfunction.

Drooling can result in perioral chapping, irritation, and maceration, with secondary infection of the facial skin, dehydration due to chronic loss of fluids, and increased risk of silent saliva aspiration that can result in recurrent respiratory infections.

Treatment options explored to control drooling in children and adults include behavioural approaches, such as prompts to swallow or wipe or preventing individuals from putting their fingers or objects into their mouths; surgery to decrease salivary flow and anticholinergic agents such as glycopyrronium.

Clinical overview and clinical summaries
The pharmacological, pharmacokinetic, efficacy and safety properties of glycopyrronium bromide are well known. A clinical overview of these aspect based on a literature review is, thus, appropriate. The clinical overview submitted is satisfactory and the literature search methodology is acceptable.

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 is a quaternary ammonium antimuscarinic with peripheral effects similar to atropine.

Antimuscarinics are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves. They also inhibit the action of acetylcholine where smooth muscle lacks cholinergic innervation.

Salivation is primarily mediated by parasympathetic innervation of the salivary glands. Glycopyrronium competitively inhibits cholinergic muscarinic receptors in salivary glands and other peripheral tissues, thus indirectly reducing the rate of salivation.

Glycopyrronium has little effect on cholinergic stimuli at nicotinic acetylcholine receptors, on structures innervated by postganglionic cholinergic neurons, and on smooth muscles that respond to acetylcholine but have no cholinergic innervation.

Peripheral antimuscarinic effects that are produced as the dose increases are: decreased production of secretions from the salivary, bronchial and sweat glands; dilatation of the pupils (mydriasis) and paralysis of accommodation (cyclopegia); increased heart rate; inhibition of micturition and reduction in gastrointestinal tone; inhibition of gastric acid secretion."

Pharmacokinetics

Bioequivalence studies
The MAH initially submitted an open-label, randomised, single-dose, three-treatment, three-period crossover study comparing the bioavailability of a glycopyrronium oral solution (10mL;1 mg/5 mL) to the marketed tablet product Robinul (Glycopyrrolate Tablets 2 mg).

However, following CHM advice, MHRA guidance and taking into account the following:

a. Robinul Forte was used in two published clinical studies that the MAH identified as pivotal, however, in the studies there is no mention of intact Robinul tablets being administered. In one study, the tablets were ground up into powder and then encapsulated. If the child could not swallow a capsule, the powder was placed in their food. In another study, no information is given on how the dose was administered, but 85% of patients were 'mentally retarded' and 58% needed 'gastrotomy tube for feeding'.

The MAH submitted a new bioequivalence 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 (Kinedexe UK Limited) 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 are presented below:

Table: Bioequivalence evaluation

Parameters	Geometric Least Square Mean		Ratio (T Vs R) (%)	% ISCV	Power (%)	The 90% confidence Intervals (%)
	T	R				
Ln (C_{max}) (pg./mL)	542.982	510.332	106.40	38.52	99.90	98.52 - 114.91
Ln (AUC_{0-t}) (hr*pg./mL)	2645.737	2524.977	104.78	32.77	99.96	97.37 - 112.76

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.

The MAH requested a 'biowaiver of additional strength' for the 1mg tablet. In support of biowaiver, the MAH provided satisfactory data to support linear pharmacokinetics. As the additional strength of the product met 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 1mg strength.

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

"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.

The bioavailability of oral glycopyrronium in children was 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 more than 90% of the radiolabel disappeared from the 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 not specified) 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(s), 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 in the age range 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 significant shorter elimination half-life (t½, z) 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 detectable 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 being 0.83 ± 0.27 hours after i.v. administration, 75 minutes after i.m. administration and in the region of 2.5 - 4 h after oral (solution) administration, though again this was highly variable. That the latter two half-lives, and especially that for oral administration, are longer than for i.v. administration probably reflects 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 (known as flip-flop kinetics, characterized by Ka < Ke).

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. As this exceeds the glomerular filtration rate and it appears that 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 secretion by the base secretory mechanism.

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 ≥30mL/min/1.73m^2) and up to 2.2 fold in subjects with severe renal impairment or end stage renal disease (estimated GFR <30 mL/min/1.73m^2). A 30% dose reduction (see section 4.2) 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.

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)."

Clinical efficacy
The MAH cited the relevant data from the literature to support the efficacy of glycopyrronium in the proposed indication. The bioequivalence 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 includes patients with a treatment duration of 8 weeks. There is no placebo or comparator controlled data beyond 8 weeks.

Zeller et al 2012a evaluated the efficacy of glycopyrronium bromide oral solution (1 mg/5 mL) in managing problem drooling associated with cerebral palsy and other neurologic conditions. Thirty-eight patients aged 3–23 years weighing at least 27 lb (12.2 kg) with severe drooling (clothing damp 5–7 days/week) were randomized to eight-weeks treatment with glycopyrronium (n = 20), 20-100 µg/kg (not exceeding 3 mg in total) three times a day, or matching placebo (n = 18). The first four weeks were an individual titration period in fixed steps depending on response followed by 4-weeks maintenance treatment. 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 which rendered 19 patients in the glycopyrrolate oral solution group an 17 in the placebo group. Responder rate was defined as at least a 3-point improvement in modified Teacher's Drooling Scale (mTDS).

Responder rate at week 8	*At least a 3-point improvement in mTDS*	*Mean improvements 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*

In addition, 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.

The safety and efficacy of glycopyrronium have been studied in an open labelled study with no control group over a 24-week period in children aged 3 to 18 years. At the week 24/exit visit, 52.3% (95% confidence interval 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. The adverse event profile was consistent with the one 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 bioequivalence study comparing the MAH's product against Cuvposa acted as a 'bridge to the literature'. The MAH provided CPRD data as useful supplementary evidence of glycopyrronium's safety in the proposed indication. 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(s) or to any of the excipients listed in section 6.1.
In common with other antimuscarinics:
Pregnancy and breast-feeding.
Angle-closure glaucoma
Myasthenia gravis (large doses of quaternary ammonium compounds have been shown to antagonise end plate nicotinic receptors)
History of intestinal obstruction
Paralytic ileus
Ulcerative colitis
Pyloric stenosis
Urinary retention
Prostatic enlargement
Severe renal impairment (eGFR <30 ml/min/1.73m^2), including those with end-stage renal disease requiring dialysis.
Concomitant treatment with (see section 4.5);

- *potassium chloride solid oral dose products;*
- *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:

<u>Management of important anticholinergic side effects</u>
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 evaluating the event, the prescriber will decide if treatment should remain stopped or if this should continue at a lower dose.

Lack of long-term safety data
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.

Mild to moderate sialorrhoea
Due to the low potential 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.

Central nervous system adverse events
Increased central nervous system effects have been reported in clinical trials including: irritability; drowsiness; restlessness; over activity; 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 patients with compromised blood brain barrier e.g. intraventricular shunt, brain tumour, encephalitis.

Children below the age of 3 years
Glycopyrronium bromide is not recommended 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."

"***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. "

"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 list 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 3). 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).

List of Adverse Reaction Frequency

Adverse reaction	***Frequency category***
Infections and infestations	
Upper respiratory infection	*Common*
Pneumonia	*Common*
Urinary tract infection	*Common*
Psychiatric disorders	

Irritability	*Very common*
Agitation	*Common*
Drowsiness	*Common*
Restlessness	*Not known*
Over activity	*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*
Pseudo-obstruction	*Uncommon*
Gastrointestinal mobility disorder	*Uncommon*
Oesophageal candidiasis	*Uncommon*
Nausea	*Not known*
Skin and subcutaneous tissue disorders	
Rash	*Common*
Dryness of 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."

Clinical assessor's overall conclusion on efficacy and safety
Based on the review of the data on safety and efficacy, this Type II Variation to

introduce a change in therapeutic indication for Glycopyrronium Bromide 1mg and 2mg Tablets, following a CHM referral which determined that the efficacy data supporting the MA are insufficient to establish the efficacy of glycopyrronium as add-on therapy in the treatment of peptic ulcer. The new indication is Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older. As a consequence, the PIL and sections 2, section 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC have been updated.

is considered approvable.

Product literature
In accordance with Directive 2010/84/EU (regulation 203(2) of The Human Medicines Regulation 2012, as amended), the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional risks and safety measures have been proposed:

V.2 Additional Risk Minimisation Measure

V.2.1 Additional risk minimisation 1 : Healthcare Professional (HCP) Checklist

Table 4: HEALTHCARE PROFESSIONAL (HCP) CHECKLIST

Objectives:	• To provide information on the administration of Glycopyrronium Bromide 1mg and 2 mg tablets, specifically on the accurate use of the prescribed dosing, the time of administration before meals, the avoidance of the administration of Glycopyrronium Bromide with high fat meals. • To provide information on the minimisation and management of anticholinergic reactions such as constipation, urinary retention, pneumonia, overheating, CNS effects or overdose, allergic reactions. • To educate the patient's caregiver about the essential information pertaining to dose directions, recommended observations of the patient, recognition of side effects and when to contact the doctor.
Rationale for the additional risk minimisation activity:	• The healthcare professional (HCP) checklist is an aid to help HCPs evaluate and discuss the risks associated with glycopyrronium bromide tablets with the patient carer. • It provides important information on the management and minimisation of side effects.
Target audience and planned distribution path:	**Target audience:** HCPs **Planned distribution path:** The HCP check list will be made available on the company website. HCP can download the checklist at the time of initiation of dose.
Plans to evaluate the effectiveness of the interventions and criteria for success:	
How effectiveness will be measured	• Routine Pharmacovigilance activities as per applicable legislation • PSURs in accordance with the timelines reported in the EURD list for glycopyrronium products indicated for the treatment of severe sialorrhea (EURD: 29-July-2020)
Criteria for judging the success of the proposed risk minimisation measures	Impact on long term use of glycopyrronium beyond 24 weeks, use in pregnancy and outcomes, use in the elderly, off label use

	including children less than 3 years and use in patients with mild to moderate sialorrhea.
Milestones for reporting	Decrease in severity, specificity, or frequency of risk

V.2.2 Additional risk minimisation 2 : Patient Alert Card — For Caregiver

Table 5: PATIENT ALERT CARD

Objectives:	• To provide essential information on the administration on glycopyrronium bromide tablets • To provide dose directions, recommended observations of the patient, recognition of side effects especially patients with neurologic problems ☐ Constipation (difficulty in passing stool) ☐ Urinary 22etention (difficulty in passing urine) ☐ Pneumonia (severe chest infection) ☐ Allergic reaction (rash, itching, red raised itchy rash (hives), difficulty in breathing or swallowing, dizziness) • 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.
Rationale for the additional risk minimisation activity:	• Detection of anticholinergic reactions in the treated population and the need to decrease the dose in case of suspicion of adverse drug reactions and contact the physician. • To avoid exposure to hot weather and overheating • Risk of caries associated with reduced salivation and need for regular dental hygiene and dental checks • To check the pulse at regular intervals
Target audience and planned distribution path:	**Target audience:** Patient's caregiver **Planned distribution path:** The patient alert card will be made available on the company website. The patient caregiver can download the

	alert card when required. The patient alert card will also be made available in the product pack.
Plans to evaluate the effectiveness of the interventions and criteria for success:	
How effectiveness will be measured	• Routine Pharmacovigilance activities as per applicable legislation • PSURs in accordance with the timelines reported in the EURD list for glycopyrronium products indicated for the treatment of severe sialorrhea (EURD: 29-July-2020)
Criteria for judging the success of the proposed risk minimisation measures	Impact on long term use of glycopyrronium beyond 24 weeks, use in pregnancy and outcomes, use in the elderly, off label use including children less than 3 years and use in patients with mild to moderate sialorrhea.
Milestones for reporting	Decrease in severity, specificity, or frequency of risk

This authorisation is conditional upon the following condition(s) being met according to the resolution date(s) shown:
Prior to the marketing of 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: 08/12/2025

This is acceptable.

BENEFIT-RISK ASSESSMENT

Benefit-risk balance

The Benefit-risk balance is 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.

Decision: Grant

Date: 17 December 2020.