Public Assessment Report

UKPAR

Glycopyrronium Bromide 1mg Tablets
Glycopyrronium Bromide 2mg Tablets

(Glycopyrronium bromide)

UK Licence Numbers: PL 44710/0017-0018

Kinedexe UK Ltd
LAY SUMMARY

Glycopyrronium Bromide 1mg and 2mg Tablets
(Glycopyrronium bromide, tablet, 1mg and 2mg)

This is a summary of the Public Assessment Report (PAR) for Glycopyrronium Bromide 1mg Tablets (PL 44710/0017) and Glycopyrronium Bromide 2mg Tablets (PL 44710/0018). It explains how Glycopyrronium Bromide 1mg and 2mg Tablets 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 Glycopyrronium Bromide 1mg and 2mg Tablets.

The products will collectively be referred to as Glycopyrronium Bromide Tablets throughout the remainder of this public assessment report.

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?
Glycopyrronium Bromide Tablets are a medicine with ‘well established use’. This means that the medicinal use of the active substance, glycopyrronium bromide, is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Glycopyrronium Bromide Tablets are used with other medicines to make the stomach contents less acidic and to help treat peptic (stomach) ulcers in adults.

How do Glycopyrronium Bromide Tablets work?
Glycopyrronium bromide (the active substance in Glycopyrronium Bromide Tablets) belongs to a group of medicines called anticholinergics or antimuscarinics. It makes the stomach contents less acidic.

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

The patient should follow their doctor’s instructions exactly. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose for adults is:

**Glycopyrronium Bromide 1 mg Tablets:**
One tablet **three times** daily (in the morning, early afternoon, and at bedtime). Some patients may require two tablets at bedtime to control the symptoms overnight.
When the patient’s symptoms are controlled, a dose of one tablet twice a day may be sufficient.
The score line is **not** intended for breaking the tablet.

**Glycopyrronium Bromide 2 mg Tablets:**
One tablet **two or three times** a day at equally spaced intervals.
The score line is **not** intended for breaking the tablet.

**Children must not take this medicine.**

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the
route of administration and the duration of treatment. Glycopyrronium Bromide Tablets can only be obtained with a prescription.

**What benefits of Glycopyrronium Bromide Tablets have been shown in studies?**
As glycopyrronium bromide is a well-known substance, and its use in the treatment of peptic ulcers in adults is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of glycopyrronium bromide for the treatment of peptic ulcers in adults.

**What are the possible side effects of Glycopyrronium Bromide Tablets?**
Like all medicines, Glycopyrronium Bromide Tablets can cause side effects, although not everybody gets them.

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?**
The MHRA decided that the benefits of Glycopyrronium Bromide Tablets are greater than their risks and recommended that they be approved for use.

**What measures are being taken to ensure the safe and effective use of Glycopyrronium Bromide Tablets?**
A Risk Management Plan 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 Summaries of Product Characteristics and the package leaflet for Glycopyrronium Bromide Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

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

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

The full PAR for Glycopyrronium Bromide Tablets follows this summary.

For more information about treatment with Glycopyrronium Bromide Tablets, read the package leaflet, or contact your doctor, dentist or pharmacist.

This summary was last updated in May 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Kinedexe UK Ltd Marketing Authorisations for the medicinal products Glycopyrronium Bromide 1mg Tablets (PL 44710/0017) and Glycopyrronium Bromide 2mg Tablets (PL 44710/0018) on 20 April 2016. The products are prescription only medicines (POM) indicated for use in adults as add-on therapy in the treatment of peptic ulcer.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing an active substance of well-established use.

Glycopyrronium bromide is a quaternary ammonium antimuscarinic agent and like other anticholinergic agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and to a limited degree in the autonomic ganglia. Thus it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions. Glycopyrronium bromide antagonises muscarinic symptoms (e.g. bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.

The highly polar quaternary ammonium group of glycopyrronium bromide limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to atropine sulphate and scopolamine hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily.

Bibliographic data on glycopyrronium bromide have been submitted to support these applications. No new non-clinical or clinical studies were conducted for these applications, which is acceptable given that these are bibliographic applications for products containing an active ingredient of well-established use.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 1mg or 2mg of glycopyrronium bromide. Other ingredients consist of the following pharmaceutical 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.

II.2. Drug Substance

INN: Glycopyrronium bromide
Chemical name: (3RS)-3-[(2SR)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide.

Structure:

\[
\text{Molecular formula: } \text{C}_{19}\text{H}_{28}\text{BrNO}_{3} \\
\text{Molecular weight: } 398.3 \text{ g/mol} \\
\text{Description: White or almost white, crystalline powder.} \\
\text{Solubility: Freely soluble in water, soluble in ethanol (96 per cent), very slightly soluble in methylene chloride.}
\]

Glycopyrronium bromide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, glycopyrronium bromide, are covered by the 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. Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, tablets containing 1mg or 2mg glycopyrronium bromide per tablet.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.
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.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

**Finished Product Specifications**
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened bottle with no special storage conditions. 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**
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of glycopyrronium bromide are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
The introduction of the generic products, Glycopyrronium Bromide 1mg and 2mg Tablets, onto the market is unlikely to result in an increase in the combined sales of glycopyrronium bromide-containing products, which in turn is unlikely to lead to an increased exposure of the environment to glycopyrronium bromide. An environmental risk assessment is therefore not deemed necessary.

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.

There are no objections to the approval of these applications from a non-clinical viewpoint.

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 stereoisometric 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 ($C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ of 6.3 (1.5) ng/mL and $T_{\text{max}}$ 10 (3.8) minutes. The respective AUC value from 0 to 8 hours was 5.61 (1.27) ng.h/mL.

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Glycopyrrolate liquid 2 mg (1 mg/5 mL) fasted</th>
<th>Robinul® tablet 2 mg (2 x 1 mg) fasted</th>
<th>Glycopyrrolate liquid 2 mg (1 mg/5 mL) fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>0.318±0.189(37)</td>
<td>0.406±0.197(37)</td>
<td>0.084±0.081(36)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>2.53(37) (0.50-6.00)</td>
<td>3.00(37) (1.50-6.00)</td>
<td>2.50(36) (1.00-6.08)</td>
</tr>
<tr>
<td>AUC$_{24h}$ (h x ng/mL)</td>
<td>1.74±1.07(37)</td>
<td>2.34±1.03(37)</td>
<td>0.38±0.14(36)</td>
</tr>
<tr>
<td>AUC$_{0-24h}$ (h x ng/mL)</td>
<td>1.81±1.09(37)</td>
<td>2.45±1.15(36)</td>
<td>0.46±0.13(35)</td>
</tr>
<tr>
<td>$\chi^2$ (h)</td>
<td>0.262±0.0965</td>
<td>0.252±0.1025(36)</td>
<td>0.232±0.055(35)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>3.02±1.20(37)</td>
<td>3.31±1.57(37)</td>
<td>3.21±1.05(35)</td>
</tr>
</tbody>
</table>

*Arithmetic mean±standard deviation (N) except for $T_{\text{max}}$ for which the median (N)(range) is reported.

The food effect data indicate the mean $C_{\text{max}}$ under fed (high fat meal) conditions is about 74% lower than the $C_{\text{max}}$ 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...
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 antispasmodic 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:
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. This is appropriate for a well-established use application.

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 it 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) and Pharmacovigilance system
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Glycopyrronium Bromide Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns as approved in the RMP:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
</tr>
<tr>
<td>• Loss of vision in patients with narrow angle glaucoma (increased pressure in the eye)</td>
</tr>
<tr>
<td>• Retention of urine in patients with prostatic hypertrophy (an enlarged prostate gland)</td>
</tr>
<tr>
<td>• Intestinal obstruction (paralytic ileus) in patients with pyloric stenosis (obstruction of the stomach) or bowel obstruction (causing vomiting, abdominal pain and swelling)</td>
</tr>
<tr>
<td>• Cardiac arrhythmias (irregular heartbeats) in patient with previous heart disease or rapid or irregular heartbeats and in patients about to have inhalational anaesthesia</td>
</tr>
<tr>
<td>• Muscular weakness and fatigue in patients with myasthenia gravis (leading to muscle weakness and fatigue)</td>
</tr>
<tr>
<td>• Inhibition of sweating; risk for patients with fever or in hot environments.</td>
</tr>
<tr>
<td>• Increased toxicity in patients with renal failure</td>
</tr>
<tr>
<td>• Reduce ability to drive or use machinery.</td>
</tr>
<tr>
<td>Important potential risks</td>
</tr>
<tr>
<td>• Use in patients with intolerance to some sugars</td>
</tr>
<tr>
<td>• Potential to alter absorption and effect of other medicinal products</td>
</tr>
<tr>
<td>• Effect on fertility</td>
</tr>
<tr>
<td>• Off-label paediatric use to reduce hypersalivation</td>
</tr>
<tr>
<td>Missing information</td>
</tr>
<tr>
<td>• Use during pregnancy and breastfeeding</td>
</tr>
<tr>
<td>• Use in children</td>
</tr>
</tbody>
</table>
Summary table of risk minimisation measures as approved in the RMP:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risk</strong> –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss of vision in patients with narrow angle glaucoma (increased pressure in the eye)</td>
<td>Details of this safety concern are included in sections 4.3, 4.5 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important identified risk</strong> –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Retention of urine in patients with prostatic hypertrophy (an enlarged prostate)</td>
<td>Details of this safety concern are included in sections 4.3 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important identified risk</strong> –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intestinal obstruction (paralytic ileus) in patients with pyloric stenosis (obstruction of the stomach) or bowel obstruction (causing vomiting, abdominal pain and swelling)</td>
<td>Details of this safety concern are included in sections 4.3 and 4.4 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important identified risk</strong> –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cardiac arrhythmias (irregular heartbeats) in patients with previous heart disease or rapid or irregular heartbeats and in patients about to have inhalational anaesthesia</td>
<td>Details of this safety concern are included in sections 4.4 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important identified risk</strong> –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Muscular weakness and fatigue in patients with myasthenia gravis (leading to muscle weakness and fatigue)</td>
<td>Details of this safety concern are included in sections 4.3 and 4.4 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important identified risk</strong> –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inhibition of sweating; risk for patients with fever or in hot environments.</td>
<td>Details of this safety concern are included in sections 4.4 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important identified risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Details of this safety concern</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
### 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 package leaflet 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, as amended. The language used for

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased toxicity in patients with renal failure</td>
<td>are included in section 4.4 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td></td>
</tr>
<tr>
<td><strong>Important identified risk</strong></td>
<td>Details of this safety concern are included in section 4.7 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td>• Reduce ability to drive or use machinery.</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Important potential risk</strong></td>
<td>Details of this safety concern are included in section 4.4 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td>• Use in patients intolerance to some sugars</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Important potential risk</strong></td>
<td>Details of this safety concern are included in section 4.5 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td>• Potential to alter absorption and effect of other medicinal products</td>
<td>Details of this safety concern are included in sections 4.6 and 5.3 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Important potential risk</strong></td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>• Effect on fertility</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Important potential risk</strong></td>
<td>Prescriber to be aware of off-label prescribing</td>
<td></td>
</tr>
<tr>
<td>• Off-label paediatric use to reduce hypersecretion</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Missing information –</strong></td>
<td>Details of this safety concern are included in section 4.6 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td>• Use during pregnancy and breastfeeding</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Missing information –</strong></td>
<td>Details of this safety concern are included in sections 4.2 and 4.4 of the SmPC and appropriate advice for patients is provided in the PIL</td>
<td>None proposed</td>
</tr>
<tr>
<td>• Use in children</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with glycopyrronium bromide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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

The approved labelling for Glycopyrronium Bromide Tablets is presented below:
PAR Glycopyrronium Bromide 1mg & 2mg 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.

For 30cc bottle carton

Glycopyrronium Bromide 1mg Tablets
100 tablets

Glycopyrronium Bromide 2mg Tablets
100 tablets

PL 44710/0017
Kinedex UK Limited
Unit 15 Moorcraft
Harlington Road
Uxbridge
UB8 3HD
UK

PL 44710/0017
Kinedex UK Limited
Unit 15 Moorcraft
Harlington Road
Uxbridge
UB8 3HD
UK

KinedexE

19
PAR Glycopyrronium Bromide 1mg & 2mg Tablets

Glycopyrronium Bromide
2mg Tablets
30 tablets

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.

After first opening: 3 months.

Kinedex
PL 44710/0018
Kinedex UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge UB8 3HD, UK