RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	Glycopyrronium Bromide
Pharmaco-therapeutic group (ATC Code):	Glycopyrronium is an antimuscarinic, ATC code: A03AB02
Name of Marketing Authorisation Holder or Applicant:	Kinedexe UK Limited
Number of medicinal products to which this RMP refers:	Two products – Glycopyrronium Bromide 1 mg Tablets Glycopyrronium Bromide 2 mg Tablets
Product(s) concerned (brand name(s)):	Glycopyrronium Bromide 1 mg Tablets Glycopyrronium Bromide 2 mg Tablets

Data lock point for this RMP	05th Oct 2020	Version number	1.8
Date of final sign off	03rd Dec 2020		

RMP version to be assessed as part of this application:

RMP Version number:	1.8
Data lock point for this RMP:	05th October 2020
Date of final sign off:	03rd December 2020
Rationale for submitting an updated RMP:	Current licence for Glycopyrronium Bromide with indication peptic ulcer has been withdrawn and new indication symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adults with chronic neurological disorders has been added. In response to the RFI received from Commission on Human Medicines (CHM) In response to the RFI received from MHRA
Summary of significant changes in this RMP:	RMP updated with current indication of symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adults with chronic neurological disorders. RMP updated in response to the concerns raised in RFI from Commission on Human Medicines (CHM). RMP updated further to update to SmPC RMP updated further to update to SmPC recommended by MHRA RMP updated further to update to SmPC and recommendations by MHRA

Other RMP versions under evaluation:

RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable

QPPV name: [redacted]

QPPV signature: [redacted]

Table of content

Part I: Product(s) Overview

Brief description of the product including: • chemical class	3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidinium bromide
• summary of mode of action	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 antagonizes muscarinic symptoms (e.g. bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.
• important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	n/a
Indication(s) in the EEA Proposed	***4.1 Therapeutic indications*** Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older.
Posology and route of administration in the EEA Proposed	1.C ***Posology and method of administration*** ***Glycopyrronium Bromide 1mg Tablets***

Posology

Glycopyrronium bromide tablets are recommended for short-term intermittent use (see section 4.4 and 5.1).

Glycopyrronium bromide tablets should be prescribed by physicians experienced in the treatment of patients with neurological disorders.

Paediatric population – children and adolescents aged 3 years and older

The dosing schedule for Glycopyrronium bromide tablets is based on the weight of the child with the initial dosing of 0.02 mg/kg to be given orally three times daily and titrate in increments of 0.02 mg/kg every 5-7 days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily not to exceed 1.5-3 mg per dose based upon weight. For greater detail, see Table 1.

During the four-week titration period, dosing can be increased with the recommended dose titration schedule while ensuring that the anticholinergic adverse events are tolerable. Prior to each increase in dose, review the tolerability of the current dose level with the patient's caregiver.

Younger children may be more susceptible to adverse events and this should be kept in mind when dose adjustments are carried out.

Following the dose titration period, the child's sialorrhoea should be monitored, in conjunction with the carer at no longer than 3 monthly intervals, to assess changes in efficacy and/or tolerability over time, and the dose adjusted accordingly.

Table 1: Dosing tables for children and adolescents aged 3 years and older

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

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

Paediatric population – children aged < 3 years

Glycopyrronium bromide tablets are not recommended for use in children younger than 3 years.

Elderly population

The elderly have a longer elimination half-life and reduced medicinal product clearance as well as limited data to support efficacy in short-term use. As such glycopyrronium bromide tablets should not be used in patients over the age of 65 years.

Adult population

For adolescents with chronic neurological disorders of childhood onset, their stable dose of glycopyrronium bromide tablets can be continued into adulthood. For adults with chronic neurological disorders of childhood onset who are initiating glycopyrronium bromide tablets, the dosing schedule described under the paediatric population subheading and summarised in Table 1 should be followed.

Renal Impairment

Elimination of glycopyrronium is severely impaired in patients with renal failure. Glycopyrronium is contraindicated in those with severe renal failure (see section 4.3).

For patients with Mild to moderate renal impairment (eGFR <90 - ≥30 ml/min/1.73m2) doses should be reduced by 30%.

Hepatic impairment

Clinical studies have not been conducted in patients with hepatic impairment. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion and hepatic impairment is not thought to result in a clinically relevant increase in systemic exposure of glycopyrronium.Other licensed glycopyrronium products are not all interchangeable on a milligram-for-milligram basis due to differences in bioavailability; please refer to the approved posology of the product if changing between products.

	Method of administration For oral administration only. For patients who cannot swallow tablets, other pharmaceutical forms should be used. Co-administration with food results in a marked decrease in systemic medicinal product exposure. Dosing should be at least one hour before or at least two hours after meals or at consistent times with respect to food intake. High fat food should be avoided. Where the patient's specific needs determine that co-administration with food is required, dosing of the medicinal product should be consistently performed during food intake (see section 5.2).
Pharmaceutical form(s) and strengths Proposed	1 mg tablets and 2 mg tablets

Country and date of first authorisation worldwide	n/a
Country and date of first launch worldwide	n/a
Country and date of first authorisation in the EEA	n/a

Is the product subject to additional monitoring in the EU? Yes ☐ No ☒

Part II: SAFETY SPECIFICATION

In accordance with Section V.C.1.1.5 [Article 10 (a) of Directive 2001/83/EC] of the Guideline on GVP Module V – Risk management systems (EMA/838713/2011 Rev 2; effective date 31 March 2017), modules SI to SVII of this RMP have been omitted.

Part II: Module SVIII — Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) • Aggravation of pyloric stenosis and paralytic ileus • Urinary retention • Constipation • Reduced bronchial secretions • Pneumonia • Interactions with other medicinal products
Important potential risks	• Use in patients with ulcerative colitis • Drug-drug/food interaction leading to altered absorption and effect on other medicinal products • Risk in elderly patients • Risk in patients with uraemia • Risk in patients with intolerance to some sugars • Overdose • Allergic reaction

Summary of safety concerns	
	• Use in patients with cardiac disorders • Dental caries with reduced salivary production • CNS effects
Missing information	• Use in pregnancy and lactation • Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea • Safety in long term use beyond 24 weeks

Part III: Pharmacovigilance Plan (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires:

Not applicable

- Other forms of routine pharmacovigilance activities:

Not applicable

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned for this product.

III.3 Summary Table of additional pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

This section has been omitted as there are no imposed or other post-authorisation efficacy studies.

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Table 1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
• Risk of overheating in patients with fever or in hot environment	**Routine risk communication:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • Patient information leaflet (PIL) sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery)	**Routine risk communication:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Due to the potential change to normal heart rhythm, glycopyrronium bromide should be used with caution in patients receiving inhalation anaesthesia, is included in SmPC sections 4.4
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant

	closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Aggravation of pyloric stenosis and paralytic ileus	**Routine risk communication:** • SmPC sections 4.3, 4.4 and 4.5 • PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation to monitor the patients for potentially excessive or prolonged constipation, during concomitant use of opioids, is included in SmPC section 4.5.
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Urinary retention	**Routine risk communication:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine

Constipation	**Routine risk communication:** • SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Reduced bronchial secretions	**Routine risk communication:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Pneumonia	**Routine risk communication:** • SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• Recommendation for physicians to discontinue glycopyrronium treatment if pneumonia occurs, is included in SmPC sections 4.4
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Interactions with other medicinal products	**Routine risk communication:** • SmPC sections 4.5, and PIL sections 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for patients to inform their treating physicians to provide information on treatment with any other medications, is included in SmPC sections 4.5
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Important potential risks	
Use in patients with ulcerative colitis	**Routine risk communication:** • SmPC sections 4.3 and 4.4 • PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information:

	• Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Drug-drug/food interaction leading to altered absorption and effect on other medicinal products	**Routine risk communication:** • SmPC sections 4.2, 4.3, 4.5 and 5.2 • PIL sections 2 and 3
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed.Legal status: Prescription only medicine
Risk in elderly patients	**Routine risk communication:** • SmPC section 4.4 and 4.5 • PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Risk in patients with uraemia	**Routine risk communication:** • SmPC section 4.4
	Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Risk in patients with intolerance to some sugars	**Routine risk communication:** • SmPC section 4.4 • PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Overdose	**Routine risk communication:** • SmPC section 4.9 • PIL section 3
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine

Allergic reaction	**Routine risk communication:** • SmPC section 4.4, 4.5, 4.8 and 5.1 • PIL section 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for physicians and caregivers to monitor anticholinergic effects with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Use in patients with cardiac disorders	**Routine risk communication:** • SmPC section 4.4, and 4.8 and PIL section 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for physicians and caregivers to monitor pulse rates and report very fast or very slow heart rate with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 and 4.8
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Dental caries with reduced salivary production	**Routine risk communication:** • SmPC section 4.4

	• PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • An advice to the patient to brush teeth daily and have regular dental checks, is included in SmPC section 4.4 and PIL sections 2
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
CNS effects	**Routine risk communication:** • SmPC section 4.4, 4.8 and 5.1 • PIL section 2 and 4
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Missing information	
Use in pregnancy and lactation	**Routine risk communication:** • SmPC sections 4.3, 4.6 and 5.3 • PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond

	the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea	**Routine risk communication:** • SmPC section 4.2, 4.4 • PIL section 2, 3
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine
Safety in long term use beyond 24 weeks	**Routine risk communication:** • SmPC section 4.4 • PIL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None proposed
	Other routine risk minimisation measures beyond the Product Information: • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Legal status: Prescription only medicine

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

V.3 Summary of risk minimisation measures

Table 6: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
• Risk of overheating in patients with fever or in hot environment	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	
Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery)	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Due to the potential change to normal heart rhythm, glycopyrronium bromide should be used with caution in patients receiving inhalation anaesthesia, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Aggravation of pyloric stenosis and paralytic ileus	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4 and 4.5 • PIL section 2 • Recommendation to monitor the patients for potentially excessive or prolonged constipation, during concomitant use of opioids, is	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	included in SmPC section 4.5. • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures	
Urinary retention	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Constipation	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5,	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	4.8 and 5.1 • PIL sections 2 and 4 • • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Reduced bronchial secretions	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Pneumonia	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5,	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	4.8 and 5.1 • PIL sections 2 and 4 • • Recommendation for physicians to discontinue glycopyrronium treatment if pneumonia occurs, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Interactions with other medicinal products	**Routine risk minimisation measures:** • SmPC sections 4.5, • PIL sections 2 • Recommendation for patients to inform their treating physicians to provide information on treatment with any other medications, is included in SmPC sections 4.5 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Important potential risks		
Use in patients with ulcerative colitis	**Routine risk minimisation measures:**	**Routine pharmacovigilance**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• SmPC sections 4.3 and 4.4 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures	**activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Drug-drug/food interaction leading to altered absorption and effect on other medicinal products	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.5 and 5.2 • PIL sections 2 and 3 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed • Prescription only medicine **Additional risk minimisation measures:** • A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Risk in elderly patients	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.5 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures	
Risk in patients with uraemia	**Routine risk minimisation measures:** • SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Risk in patients with intolerance to some sugars	**Routine risk minimisation measures:** • SmPC sections 4.4 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Overdose	**Routine risk minimisation measures:** • SmPC section 4.9 • PIL section 3	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	None proposed **Additional pharmacovigilance activities:** None proposed
Allergic reaction	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL section 2 and 4 • • Recommendation for physicians and caregivers to monitor anticholinergic effects with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Use in patients with cardiac disorders	**Routine risk minimisation measures:** • SmPC section 4.4, and 4.8 • PIL section 2 and 4 • Recommendation for physicians and caregivers to	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	monitor pulse rates and report very fast or very slow heart rate with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 and 4.8 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**pharmacovigilance activities:** None proposed
Dental caries with reduced salivary production	**Routine risk minimisation measures:** • SmPC sections 4.4 • PIL section 2 • An advice to the patient to brush teeth daily and have regular dental checks, is included in SmPC section 4.4 and PIL sections 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
CNS effects	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.8 and 5.1	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• PIL section 2 and 4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Additional pharmacovigilance activities:** None proposed
Missing information		
Use in pregnancy and lactation	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.6 and 5.3 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed
Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea	**Routine risk minimisation measures:** • SmPC sections 4.2 and 4.4 • PIL section 2, 3 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	
Safety in long term use beyond 24 weeks	**Routine risk minimisation measures:** • SmPC sections 4.4 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** A Checklist for HCPs and Alert Card for Care Givers (see Annexes 6).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed **Additional pharmacovigilance activities:** None proposed

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Glycopyrronium Bromide 1 mg & 2 mg Tablets:

This is a summary of the risk management plan (RMP) for Glycopyrronium bromide tablets. The RMP details important risks of Glycopyrronium bromide tablets, how these risks can be minimised, and how more information will be obtained about Glycopyrronium bromide tablets risks and uncertainties (missing information).
Glycopyrronium bromide tablets summary of product characteristics (SmPC) and package leaflet (PL) give essential information to healthcare professionals and patients on how Glycopyrronium bromide tablets should be used.
Important new concerns or changes to the current ones will be included in updates of Glycopyrronium bromide tablets RMP.

1. The medicine and what it is used for

Glycopyrronium bromide tablet is indicated for symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older.

The tablet product is unsuitable for younger children (under approximately 31kg), for this patient population other pharmaceutical forms should be used.

Glycopyrronium bromide tablets contain glycopyrronium bromide as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Glycopyrronium bromide tablets, together with measures to minimise such risks and the proposed studies for learning more about Glycopyrronium bromide tablets, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size- the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status- the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In the case of Glycopyrronium bromide tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Glycopyrronium bromide tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Glycopyrronium bromide tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Glycopyrronium bromide tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with heart problems including heart attack, high blood pressure, damaged blood vessel that supply blood to the heart and irregular heartbeats, this can be caused by conditions such as an overactive thyroid gland, heart failure or heart surgery) (Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery)) • Worsening of a condition that causes narrowing of the opening from the stomach to the small gut and stoppage of gut movement due to paralysis of the muscles in the gut (Aggravation of pyloric stenosis and paralytic ileus) • Inability to completely empty the bladder (Urinary retention) • Constipation • Reduced bronchial secretions • Pneumonia • Using other medications with Glycopyrronium tablets (Interactions with other medicinal products)
Important potential risks	• Use in patients with inflammation of the

	intestine (Use in patients with ulcerative colitis) • Altered absorption and effect on other medicinal products due to interaction with other drugs or foods (Drug-drug/food interaction leading to altered absorption and effect on other medicinal products) • Risk in elderly patients • Risk in patients with abnormally high level of waste products in blood (Risk in patients with uraemia) • Risk in patients with intolerance to some sugars • Excess intake of this medicine (Overdose) • Allergic reaction • Use in patients with heart conditions (cardiac disorders) • Dental caries with reduced salivary production • CNS effects
Missing information	• Use during pregnancy and breastfeeding (Use in pregnancy and lactation) • Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea • Safety in long term use beyond 24 weeks

II.B Summary of important risks

Important identified risks

Risk of overheating in patients with fever or in hot environment	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that Glycopyrronium Bromide inhibits sweating. In the presence of a high environmental temperature, heat prostration (fever and heat stroke due to decreased sweating) can occur with use of this medicine. Further, glycopyrronium may potentiate the effects of oligohidrosis and hyperthermia associated with the use of topiramate.
Risk factors and risk groups	Risk of hypohidrosis is common in patient receiving drugs from any of the following drug classes: anticholinergics, tricyclics antidepressants (medicines used to treat depression), antiepileptics (medicines for seizure),

	antihistamines (medicines for allergy), antihypertensives (medicines for high blood pressure, antipsychotics (used to treat mental problems) and antiemetics (used to treat nausea and vomiting), antivertigo drugs, bladder antispasmodics, gastric antisecretory drugs, muscle relaxants, neuromuscular paralytics, and opioids As per the SmPC Risk group include: • patients with fever Risk factor include: • high environmental temperatures
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Pack size: Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Increase in heart rate; risk in patients with heart problems including heart attack, high blood pressure, damaged blood vessel that supply blood to the heart and irregular heartbeats, this can be caused by conditions such as an overactive thyroid gland, heart failure or heart surgery) (Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery))	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that Glycopyrronium bromide produce increase in heart rate after its administration. Further, Concomitant use of inhaled anaesthetics with glycopyrronium bromide may lead to potential change to

	normal heart rhythm.
Risk factors and risk groups	Increased heart rate itself is an independent predictor of cardiovascular mortality. However, it also positively associated with cardiovascular risk factors (hypertension, diabetes mellitus, hypertriglyceridemia, alcohol and habitual exercise) and clustering of these factors. As per the SmPC, risk factors include: • Due to the potential change to normal heart rhythm, glycopyrronium bromide should be used with caution in patients receiving inhalation anaesthesia.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • A recommendation to advise to the carer to measure the pulse rate if the child seems unwell and report very fast or very slow heart rate, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Worsening of a condition that causes narrowing of the opening from the stomach to the small gut and stoppage of gut movement due to paralysis of the muscles in the gut (Aggravation of pyloric stenosis and paralytic ileus)	
Evidence for linking the risk to the medicine	SmPC mention that large doses of Glycopyrronium bromide may suppress intestinal motility to the point of producing a paralytic ileus and for this reason may precipitate or aggravate serious complication. Concomitant use of opioids may result in additive gastrointestinal adverse effects,and increase the risk of severe constipation or paralytic ileus.
Risk factors and risk groups	Risk group includes: • Patients with history of pyloric stenosis and paralytic ileus

	Risk factor includes: • Concomitant use of opioids
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4 and 4.5 • PIL section 2 • Recommendation to monitor the patients for potentially excessive or prolonged constipation, during concomitant use of opioids, is included in SmPC section 4.5. • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Inability to completely empty the bladder (Urinary retention)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention mention that urinary retention has been associated with the use of Glycopyrronium bromide. Further, many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as urine retention.
Risk factors and risk groups	Risk groups include: • Patients with urinary retention, prostatic enlargement and severe renal impairment (eGFR <30 ml/min/1.73m2), including those with end-stage renal disease requiring dialysis. Risk factor include: • Concomitant use of other antimuscarinic drugs.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 • PIL sections 2 and 4 • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes

	may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.
Constipation	
Evidence for linking the risk to the medicine	Constipation is a known side effect of anticholinergic drugs and existing constipation is likely to be exacerbated. (SmPC) Constipation was seen in 57% of children with profound multiple disabilities in specialised day-care centres and schools in Netherlands. (Veugelers R, 2010)
Risk factors and risk groups	Not known in target population
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 • PIL section 2 and 4 • Recommendation for physicians and caregivers to monitor anticholinergic effects (urinary retention, constipation and overheating) with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.
Reduced bronchial secretions	
Evidence for linking the risk to the medicine	Reduced bronchial secretions is a known side effect of anticholinergic drug. (SmPC)
Risk factors and risk groups	Not known in target population

Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.5, 4.8 and 5.1 • PIL section 2 and 4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.
Pneumonia	
Evidence for linking the risk to the medicine	Known risk in patients treated with anticholinergic drugs. (SmPC)
Risk factors and risk groups	Not known in target population
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 • PIL section 2 and 4 • Recommendation for physicians to discontinue glycopyrronium treatment if pneumonia occurs, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.
Using other medications with Glycopyrronium tablets (Interactions with other medicinal products)	
Evidence for linking the risk to the medicine	No studies have been performed and there are limited data available relating to interactions in the paediatric age group. Advice is given that concomitant use of the following drugs should be avoided: potassium chloride

	solid oral dose, topiramate, anticholinergic drugs, antispasmodic drugs
Risk factors and risk groups	Not known in target population
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.5 • PIL section 2 • Recommendation for patients to inform their treating physicians to provide information on treatment with any other medications, is included in SmPC sections 4.5 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Important potential risks

Use in patients with inflammation of the intestine (Use in patients with ulcerative colitis)	
Evidence for linking the risk to the medicine	SmPC mention that Glycopyrronium bromide tablets should be used with caution in gastro-oesophageal reflux disease, ulcerative colitis, pre-existing constipation
Risk factors and risk groups	Risk group includes: • Patients with history of intestinal obstruction, ulcerative colitis
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3 and 4.4 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Altered absorption and effect on other medicinal products due to interaction with other drugs or foods (Drug-drug/food interaction leading to altered absorption and effect on other medicinal products)	
Evidence for linking the risk to the medicine	SmPC mention that anticholinergic agents may delay absorption of other medication given concomitantly. Increased antimuscarinic side-effects: amantadine; tricyclic antidepressants; antihistamines; clozapine; disopyramide; Monoamine oxidase inhibitors (MAOIs); nefopam; pethidine; phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations). Possibly increased antimuscarinic side-effects: tricyclic (related) antidepressants. Amantadine: anticholinergic effects of Glycopyrronium bromide may be increased with concomitant administration. Antispasmodics: glycopyrronium may antagonize the pharmacological effects of gastrointestinal prokinetic active substances such as domperidone and metoclopramide. Atenolol: bioavailability may be increased with co-administration of Glycopyrronium bromide. Digoxin: may increase serum levels of digoxin (from slow release digoxin formulations). Domperidone/Metoclopramide: antagonism of the effect on gastro-intestinal activity. Haloperidol: serum levels may be decreased when co-administered with Glycopyrronium bromide resulting in worsening of schizophrenic symptoms and development of tardive dyskinesia. Ketoconazole: reduced absorption of ketoconazole. Levodopa: absorption of levodopa possibly reduced. Memantine: effects possibly enhanced by memantine. Metformin: plasma levels may be elevated with co-administration of Glycopyrronium bromide. MAOIs: these block detoxification of Glycopyrronium bromide thus potentiating its action Nitrates: possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth). Opioids: active substances such as pethidine and codeine may result in additive central nervous system (CNS) adverse effects, and increase the risk of CNS depression. Parasympathomimetics: antagonism of effect. Potassium chloride: may increase the severity of potassium chloride-induced gastrointestinal lesions as a result of a slower gastrointestinal transit time. Slower gastrointestinal time produced by Glycopyrronium bromide may increase the risk of hyperkalemia. Reserpine: Glycopyrronium bromide may antagonize the inhibitory action of Glycopyrronium bromide on gastric acid secretion. Sedating antihistamines: may have additive anticholinergic

	effects. A reduction in anticholinergic and/or antihistamine dosage may be necessary.
Risk factors and risk groups	Risk factor includes: • Concomitant use of other medicinal products or food.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.5 and 5.2 • PIL sections 2 and 3 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Risk in elderly patients	
Evidence for linking the risk to the medicine	As per the SmPC Glycopyrronium bromide should be used with caution in the elderly. Concomitant use of two or more drugs having anticholinergic effects may lead to confusion in the elderly.
Risk factors and risk groups	Risk group: • Elderly patients Risk factors: • Co-morbid conditions • Concomitant medications
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.5 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:**

	• No risk minimisation measures

Risk in patients with abnormally high level of waste products in blood (Risk in patients with uraemia)	
Evidence for linking the risk to the medicine	As per the SmPC, because of prolongation of renal elimination, repeated or large doses of glycopyrronium bromide should be avoided in patients with uraemia.
Risk factors and risk groups	Risk groups: • Uraemic patients • Patients with pre-existing renal failure
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Risk in patients with intolerance to some sugars	
Evidence for linking the risk to the medicine	As per the SmPC, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Risk factors and risk groups	Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Excess intake of this medicine (Overdose)	
Evidence for linking the risk to	SmPC of Glycopyrronium bromide mention that, there are chances of overdose, if this medicine is not used as per the

the medicine	prescribed information.
Risk factors and risk groups	Patients taking more than the prescribed dose of Glycopyrronium Bromide.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.9 • PIL section 3 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Allergic reaction	
Evidence for linking the risk to the medicine	Known risk in patients treated with anticholinergic drugs. (SmPC)
Risk factors and risk groups	• Not known in target population • Concomitant use of antihistamines
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4, 4.5, 4.8 and 5.1 • PIL section 2 and 4 • Recommendation for physicians and caregivers to monitor anticholinergic effects with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving

	Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.
Use in patients with heart conditions (cardiac disorders)	
Evidence for linking the risk to the medicine	
Risk factors and risk groups	Not known in target population
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4 and 4.8 • PIL section 2 and 4 • Recommendation for physicians and caregivers to monitor pulse rates and report very fast or very slow heart rate with adherence to the management instructions in disabled patients, is included in SmPC sections 4.4 and 4.8 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Dental caries with reduced salivary production	
Evidence for linking the risk to the medicine	Reduced salivation can increase the risk of oral cavities and periodontal diseases. (SmPC) Chronic drooling is associated with dental caries. Severe oral drying increases the risk oral cavities and periodontal diseases.
Risk factors and risk groups	Patients with severe dry mouth
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4 • PIL section 2 • An advice to the patient to brush teeth daily and have regular dental checks, is included in SmPC section 4.4 and PIL sections 2 • Tablets are proposed to be packed in a white HDPE

	bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

CNS effects	
Evidence for linking the risk to the medicine	Increased central nervous system effects have been reported in clinical trials including: irritability; drowsiness; restlessness; overactivity; short attention span; frustration; mood changes; temper outbursts or explosive behaviour; excessive sensitivity; seriousness or sadness; frequent crying episodes; fearfulness. Glycopyrronium bromide is a quaternary ammonium member of the anticholinergic class of drugs and as a consequence of its quaternary charge, has limited ability to penetrate the blood brain barrier. (SmPC)
Risk factors and risk groups	Increased risk in children with compromised blood brain barrier.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4, 4.8 and 5.1 • PIL section 2 and 4 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Missing information

Use during pregnancy and breastfeeding (Use in pregnancy and lactation)	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.6 and 5.3 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.2 and 4.4 • PIL section 2, 3 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:** • Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

Safety in long term use beyond 24 weeks	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4 • PIL section 2 • Tablets are proposed to be packed in a white HDPE bottle with a child resistant closure containing 10, 14, 28, 30, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed. • Prescription only medicine **Additional risk minimisation measures:**

	• Healthcare professional and caregivers educational cards will be made available, advising the HCP of the important points to reinforce when giving Glycopyrronium Bromide and giving detailed guidance to the carer on dosing and how to identify important side effects.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Glycopyrronium bromide tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Glycopyrronium bromide tablets.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3 — Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4 — Specific adverse drug reaction follow-up forms

Not applicable

Annex 5 — Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6 — Details of proposed additional risk minimisation activities (if applicable)

An educational program will be put in place for glycopyrronium bromide tablets. A carer information pack consisting of patient information leaflet and a patient alert card for the patient's carer and physician educational material consisting of a summary of product characteristics and checklist for the healthcare professional will be made available to aide in the accurate dosing and monitoring of anticholinergic affects

HEALTHCARE PROFESSIONAL (HCP) CHECKLIST
Glycopyrronium Bromide 1mg & 2mg Tablets

The healthcare professional (HCP) checklist is an aid to help you evaluate and discuss the risks associated with glycopyrronium bromide tablets with the patient's carer. It provides important information on the management and minimisation of side effects.

The information below is provided as a guide for the healthcare professional. For more detailed information on this product please refer to the summary of product characteristics.
For any additional enquiries about this product or if you need additional copies of the HCP checklist you may email Kinedexe.MI@primevigilance.com.

Marketing Authorisation Holder and Manufacturer: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge, UB8 3HD, United Kingdom.

MANAGEMENT AND MINIMISATION OF SIDE EFFECTS

- Glycopyrronium bromide tablets are indicated for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older.
- Due to the lack of long term safety data, glycopyrronium bromide tablets are recommended for short-term intermittent use.
- Physicians who are specialised in the treatment of patients with neurological disorders should prescribe glycopyrronium bromide tablets. The physician should also regularly monitor the patient and change the dose accordingly.
- Glycopyrronium bromide is an anticholinergic drug and the most common side effects are those typically associated with this type of treatment. These effects are often dose dependent and difficult to evaluate in a disabled child.
- The treating physician should make the patient's caregiver aware of the possible anticholinergic effects which can occur and should guide the carer on how to prevent or reduce them.
- During the treatment, anticholinergic side effects should be assessed in the patient by the treating physician. The following checklist for the assessment of anticholinergic side effects should be used.

Checklist for assessment of side effects associated with glycopyrronium bromide use.	
Patient name:	
Date of assessment:	
Anticholinergic effects	**Result of Assessment**
Constipation	
Urinary Retention	
Pneumonia	
Allergic Reaction	
Overheating	
Dental disease	
CNS effects	
Cardiovascular effects	

- The dosage of glycopyrronium bromide tablets should be adjusted to the needs of the individual patient to assure symptomatic control with a minimum of adverse reactions. To aid accurate dosing, a dosage regimen is given as part of a patient alert card for the caregiver. The patient alert card should be completed by the physician with the initial dose and any subsequent dose change.

ESSENTIAL INFORMATION ON GLYCOPYRRONIUM BROMIDE TABLETS TO BE PROVIDED TO THE PATIENT'S CAREGIVER

The patient's caregiver should be made aware of the following essential points:

- To administer glycopyrronium bromide tablets as the doctor has prescribed.
- To contact the patient's doctor if the patient's carer is not sure about the exact dose to be administered to the patient.
- To administer glycopyrronium bromide tablets at least one hour before or two hours after meals or at consistent times with respect to food intake.
- To avoid administration of glycopyrronium bromide tablets with high fat meals.
- To not increase the dose of glycopyrronium bromide tablets without the permission of the patient's doctor.
- To stop using this medicine and seek urgent medical advice if any of the following serious side effects occur.
    - Constipation (difficulty in passing stool)
    - Urinary retention (difficulty in passing urine)
    - Pneumonia (severe chest infection)
    - Allergic reaction (rash, itching, red raised itchy rash (hives), difficulty in breathing or swallowing, dizziness)
- It is sometimes difficult to detect side effects in patients with neurological problems who cannot adequately express how they feel. In these situations, if the patient's caregiver observes any side effects after increasing the dose, then they should decrease the dose to the previous one and immediately contact the treating doctor.
- To avoid overheating and the possibility of heat stroke, the patient's carer should avoid exposing the patient to hot or very warm weather. To check with the doctor during hot weather to see if the dose should be reduced.
- The risk of dental disease can increase with reduced salivation. It is important that daily dental hygiene checks and regular dental health checks are performed.
- The patient's caregiver should regularly check the patient's pulse and contact the patient's doctor if the heartbeat is very slow or rapid.
- The patient's caregiver should observe any changes in the patient's behaviour or well-being and convey the same to the patient's treating doctor.

ADDITIONAL INFORMATION TO EMPHASISE

The patient's caregiver should be made aware of the following additional points:

- To consult a doctor **immediately** or go to the emergency department of the nearest hospital right away if the patient is given more glycopyrronium bromide tablets than they should, even if the patient seems well.
- Tell the patient's doctor if they are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- To report any side effects to the healthcare professional.
- To read the Patient Information leaflet.
- To consult with the prescribing doctor at no longer than 3 monthly intervals to ensure that

glycopyrronium bromide is still an appropriate treatment for the patient.

- Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:
  - the Yellow Card website www.mhra.gov.uk/yellowcard
  - the free Yellow Card app available from Apple App Store or Google Play Store
  - some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

  Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9 am and 5 pm. You can leave a message outside of these hours.

  When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

For additional information, the patient's caregiver can also refer to the patient information leaflet provided with this product.

This HCP checklist was revised in December 2020

Healthcare Professional (HCP) Checklist – Mock-up

HEALTHCARE PROFESSIONAL (HCP) CHECKLIST
GLYCOPYRRONIUM BROMIDE 1 MG & 2 MG TABLETS

KinedexE

The healthcare professional (HCP) checklist is an aid to help you evaluate and discuss the risks associated with glycopyrronium bromide tablets with the patient's carer. It provides important information on the management and minimisation of side effects.

The information below is provided as a guide for the healthcare professional. For more detailed information on this product please refer to the summary of product characteristics.

For any additional enquiries about this product or if you need additional copies of the HCP checklist you may email Kinedexe.MI@primevigilance.com.

Marketing Authorisation Holder and Manufacturer: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge, UB8 3HD, United Kingdom.

MANAGEMENT AND MINIMISATION OF SIDE EFFECTS

- Glycopyrronium bromide tablets are indicated for the symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older.
- Due to the lack of long term safety data, glycopyrronium bromide tablets are recommended for short-term intermittent use.
- Physicians who are specialised in the treatment of patients with neurological disorders should prescribe glycopyrronium bromide tablets. The physician should also regularly monitor the patient and change the dose accordingly.
- Glycopyrronium bromide is an anticholinergic drug and the most common side effects are those typically associated with this type of treatment. These effects are often dose dependent and difficult to evaluate in a disabled child.
- The treating physician should make the patient's caregiver aware of the possible anticholinergic effects which can occur and should guide the carer on how to prevent or reduce them.
- During the treatment anticholinergic side effects should be assessed in the patient by the treating physician. The following checklist for the assessment of anticholinergic side effects should be used.

Checklist for assessment of side effects associated with glycopyrronium bromide use.	
Doctor's name:	
Date of assessment:	
Anticholinergic effects	Result of Assessment
Constipation	
Urinary Retention	
Pneumonia	
Allergic Reaction	
Overheating	
Dental disease	
CNS effects	
Cardiovascular effects	

- The dosage of glycopyrronium bromide tablets should be adjusted to the needs of the individual patient to assure symptomatic control with a minimum of adverse reactions. To aid accurate dosing, a dosage regimen is given as part of a patient alert card for the caregiver. The patient alert card should be completed by the physician with the initial dose and any subsequent dose change.

ESSENTIAL INFORMATION ON GLYCOPYRRONIUM BROMIDE TABLETS TO BE PROVIDED TO THE PATIENT'S CAREGIVER

The patient's caregiver should be made aware of the following essential points:

- To administer glycopyrronium bromide tablets as the doctor has prescribed.
- To contact the patient's doctor if the patient's carer is not sure about the exact dose to be administered to the patient.
- To administer glycopyrronium bromide tablets at least one hour before or two hours after meals or at consistent times with respect to food intake.
- To avoid administration of glycopyrronium bromide tablets with high fat meals.
- To not increase the dose of glycopyrronium bromide tablets without the permission of the patient's doctor.
- To stop using this medicine and seek urgent medical advice if any of the following serious side effects occur.
  - Constipation (difficulty in passing stool)
  - Urinary retention (difficulty in passing urine)
  - Pneumonia (severe chest infection)
  - Allergic reaction (rash, itching, red raised itchy rash (hives), difficulty in breathing or swallowing, dizziness)
- It is sometimes difficult to detect side effects in patients with neurological problems who cannot adequately express how they feel. In these situations, if the patient's caregiver observes any side effects after increasing the dose, then they should decrease the dose to the previous one and immediately contact the treating doctor.
- To avoid overheating and the possibility of heat stroke, the patient's carer should avoid exposing the patient to hot or very warm weather. To check with the doctor during hot weather to see if the dose should be reduced.
- The risk of dental disease can increase with reduced salivation. It is important that daily dental hygiene checks and regular dental health checks are performed.
- The patient's caregiver should regularly check the patient's pulse and contact the patient's doctor if the heartbeat is very slow or rapid.
- The patient's caregiver should observe any changes in the patient's behaviour or well-being and convey the same to the patient's treating doctor.

ADDITIONAL INFORMATION TO EMPHASISE

The patient's caregiver should be made aware of the following additional points:

- To consult a doctor **immediately** or go to the emergency department of the nearest hospital right away if the patient is given more glycopyrronium bromide tablets than they should, even if the patient seems well.
- Tell the patient's doctor if they are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- To report any side effects to the healthcare professional.
- To read the Patient Information leaflet.
- To consult with the prescribing doctor at no longer than 3 monthly intervals to ensure that glycopyrronium bromide is still an appropriate treatment for the patient.
- Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:
  - the Yellow Card website www.mhra.gov.uk/yellowcard
  - the free Yellow Card app available from Apple App Store or Google Play Store
  - some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9 am and 5 pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

For additional information, the patient's caregiver can also refer to the patient information leaflet provided with this product.

This HCP checklist was revised in December 2020

PATIENT ALERT CARD - FOR CARERGIVER
Glycopyrronium Bromide 1mg & 2mg Tablets

The side effects associated with glycopyrronium bromide may be dose dependent and difficult to assess in a disabled patient. The patient's doctor will talk to you about common side effects that may occur and how to manage them.

This patient alert card is an aid which helps to provide the patient's caregiver with essential information on the administration of glycopyrronium bromide tablets and the management and minimisation of side effects. It is important that this card is given to the treating doctor to record guidance on dosing.

The information below is provided as a guide for the patient's caregiver. For more detailed information on this product please refer to the patient information leaflet.
For any additional enquiries about this product or If you need additional copies of the patient alert card you may email Kinedexe.MI@primevigilance.com.

Marketing Authorisation Holder and Manufacturer: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge, UB8 3HD, United Kingdom.

ESSENTIAL INFORMATION ON THE ADMISTRATION OF GLYCOPYRRONIUM BROMIDE TABLETS

- The dosage of glycopyrronium bromide tablets should be adjusted to the needs of the individual patient to assure symptomatic control with a minimum of adverse reactions.
- Always follow the doctor's instructions when giving glycopyrronium bromide tablets. You should check with the patient's doctor if you are not sure. The dose should not be increased without consultation with the patient's doctor.
- It is important to make sure an accurate dose is given each time, in order to prevent harmful effects of glycopyrronium bromide seen with dosing errors or overdose.
- Glycopyrronium bromide tablets should be taken at least one hour before or two hours after meals. If the patient's specific needs determine that co-administration with food is required, it is important to give glycopyrronium bromide at consistent times in relation to food intake.
- Avoid administration of glycopyrronium bromide tablets with high fat meals.
- The treating doctor will complete the dosing regimen included with this patient alert card when treatment is started and at each dose change. Its purpose is to aid the patient's caregiver with respect to the correct dose to be given.

MANAGEMENT AND MINIMISATION OF SIDE EFFECTS

Like all medicines, glycopyrronium bromide tablets can cause side effects, although not everybody gets them.

If any of the following serious side effects occur, stop using the medicine and seek urgent medical advice. After evaluating the event, the prescriber will decide if treatment should remain stopped or if this should continue at a lower dose.

- Constipation (difficulty in passing stool)
- Urinary retenion (difficulty in passing urine)
- Pneumonia (severe chest infection)

- Allergic reaction (rash, itching, red raised itchy rash (hives), difficulty in breathing or swallowing, dizziness)

It can sometimes be difficult to detect side effects in patients with neurological problems who cannot easily tell you how they feel. If you feel a troublesome side effect is occurring after increasing a dose, you should decrease the dose to the previous one used and contact the treating doctor.

To avoid overheating and the possibility of heat stroke, you should avoid exposing the patient to hot or very warm temperature (hot weather, high room temperature). Check with the treating doctor during hot weather to see if the dose of this medicine should be reduced.

The risk of dental disease can increase with reduced salivation. It is important that daily dental hygiene checks and regular dental health checks are performed.

As a precaution you should regularly check the patient's pulse and contact the patient's doctor if the heartbeat is very slow or very rapid.

You should look for any changes in the patient's well-being or behaviour and tell the patient's doctor.

Please refer to the dose administration table for the correct dose to be given to the patient.

DOSE REGIMEN (be completed by treating doctor)

Patient name:		**DOB:**	
Doctor's name:			
Doctors contact details:			
No	**Dose (mg)**	**Start date (dd/mm/yy)**	**End date (dd/mm/yy)**
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
Additional comments:			

OTHER INFORMATION

- Talk with the patient's doctor **immediately** or go to the emergency department of the nearest hospital right away if the patient is given more glycopyrronium bromide tablets than they should, even if the patient seems well.
- Check with the patient's doctor at least every 3 months to make sure glycopyrronium bromide is

still right for the patient.

- Tell the patient's doctor if they are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme, via the Yellow Card website www.mhra.gov.uk/yellowcard, the free Yellow Card app available in Apple App Store or Google Play Store. Alternatively, you can call 0800 731 6789 for free, Monday to Friday between 9am and 5pm. By reporting side effects, you can help provide more information on the safety of this medicine.
- If the patient gets any side effects, talk to the patient's doctor, pharmacist or nurse.

This patient alert card was revised in November 2020

Patient Alert Card – Mock-up

PATIENT ALERT CARD - FOR CARERGIVER

GLYCOPYRRONIUM BROMIDE 1 MG & 2 MG TABLETS

KinedexE

The side effects associated with glycopyrronium bromide may be dose dependent and difficult to assess in a disabled patient. The patient's doctor will talk to you about common side effects that may occur and how to manage them.

This patient alert card is an aid which helps to provide the patient's caregiver with essential information on the administration of glycopyrronium bromide tablets and the management and minimisation of side effects. It is important that this card is given to the treating doctor to record guidance on dosing.

The information below is provided as a guide for the patient's caregiver. For more detailed information on this product please refer to the patient information leaflet.

For any additional enquiries about this product or if you need additional copies of the patient alert card you may email Kinedexe.MI@primevigilance.com.

Marketing Authorisation Holder and Manufacturer: Kinedexe UK Limited, Unit 15 Moorcroft, Harlington Road, Uxbridge, UB8 3HD, United Kingdom.

ESSENTIAL INFORMATION ON THE ADMINISTRATION OF GLYCOPYRRONIUM BROMIDE TABLETS

- The dosage of glycopyrronium bromide tablets should be adjusted to the needs of the individual patient to assure symptomatic control with a minimum of adverse reactions.
- Always follow the doctor's instructions when giving glycopyrronium bromide tablets. You should check with the patient's doctor if you are not sure. The dose should not be increased without consultation with the patient's doctor.
- It is important to make sure an accurate dose is given each time, in order to prevent harmful effects of glycopyrronium bromide seen with dosing errors or overdose.
- Glycopyrronium bromide tablets should be taken at least one hour before or two hours after meals. If the patient's specific needs determine that co-administration with food is required, it is important to give glycopyrronium bromide at consistent times in relation to food intake.
- Avoid administration of glycopyrronium bromide tablets with high fat meals.
- The treating doctor will complete the dosing regimen included with this patient alert card when treatment is started and at each dose change. Its purpose is to aid the patient's caregiver with respect to the correct dose to be given.

MANAGEMENT AND MINIMISATION OF SIDE EFFECTS

Like all medicines, glycopyrronium bromide tablets can cause side effects, although not everybody gets them.

If any of the following serious side effects occur, stop using the medicine and seek urgent medical advice. After evaluating the event, the prescriber will decide if treatment should remain stopped or if this should continue at a lower dose.

- Constipation (difficulty in passing stool)
- Urinary retention (difficulty in passing urine)
- Pneumonia (severe chest infection)
- Allergic reaction (rash, itching, red raised itchy rash (hives), difficulty in breathing or swallowing, dizziness)

It can sometimes be difficult to detect side effects in patients with neurological problems who cannot easily tell you how they feel. If you feel a troublesome side effect is occurring after increasing a dose, you should decrease the dose to the previous one used and contact the patient's doctor.

To avoid overheating and the possibility of heat stroke, you should avoid exposing the patient to hot or very warm temperature (hot weather, high room temperature). Check with the treating doctor during hot weather to see if the dose of this medicine should be reduced.

The risk of dental disease can increase with reduced salivation. It is important that daily dental hygiene checks and regular dental health checks are performed.

As a precaution you should regularly check the patient's pulse and contact the patient's doctor if the heartbeat is very slow or very rapid.

You should look for any changes in the patient's well-being or behaviour and tell the patient's doctor.

Please refer to the dose administration table for the correct dose to be given to the patient.

DOSE REGIMEN (be completed by treating doctor)

Patient name:			DOB:
Doctor's name:			
Doctors contact details:			
No	Dose (mg)	Start date (dd/mm/yy)	End date (dd/mm/yy)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
Additional comments:			

OTHER INFORMATION

- Talk with the patient's doctor **immediately** or go to the emergency department of the nearest hospital right away if the patient is given more glycopyrronium bromide tablets than they should, even if the patient seems well.
- Check with the patient's doctor at least every 3 months to make sure glycopyrronium bromide is still right for the patient.
- Tell the patient's doctor if they are taking or have recently taken any other medicines, including medicines obtained without a prescription.
- Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme, via the Yellow Card website www.mhra.gov.uk/yellowcard, the free Yellow Card app available in Apple App Store or Google Play Store. Alternatively, you can call 0800 731 6789 for free, Monday to Friday between 9am and 5pm. By reporting side effects, you can help provide more information on the safety of this medicine.
- If the patient gets any side effects, talk to the patient's doctor, pharmacist or nurse.

This patient alert card was revised in November 2020

Annex 7 — Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
1.2	awaiting approval	Current licence for Glycopyrronium Bromide with indication peptic ulcer has been withdrawn and new indication symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adults with chronic neurological disorders has been added. RMP updated with current indication of symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adults with chronic neurological disorders.
1.3	awaiting approval	RMP updated in response to the concerns raised in RFI from Commission on Human Medicines (CHM). Following information added • Healthcare Professional (HCP) Checklist, help HCPs to evaluate and discuss the risks associated with glycopyrronium bromide tablets with the patient carer. • Patient Alert Card, a detailed guidance to the carer on dosing and how to identify important side effects. • Important identified risks: (a) Constipation (b) Reduced bronchial secretions (c) Pneumonia • Important potential risks: (a) Allergic reaction (b) Dental caries with reduced salivary production (c) CNS effects

		• Important missing information: (a) Safety in long term use beyond 24 weeks • Important identified risk 'Inhibition of sweating: risk in patients with fever or in high temperature environments' is renamed to 'Risk of overheating in patients with fever or in hot environments' • Important missing information 'Use in children' is revised to 'Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea' • Safety concerns removed from previous version: • effects on ability to drive or use machinery; angle closure glaucoma; aggravation of myasthenia gravis; effect on fertility • Risk minimization measures updated according to the amendments to the list of safety concerns.
1.4	awaiting approval	RMP updated further to update to SmPC and PIL Important Identified Risks • Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) • Aggravation of pyloric

		stenosis and paralytic ileus • Urinary retention • Constipation • Reduced bronchial secretions • Pneumonia Important Potential Risks • Use in patients with ulcerative colitis • Drug-drug/food interaction leading to altered absorption and effect on other medicinal products • Risk in elderly patients • Risk in patients with uraemia • Risk in patients with intolerance to some sugars • Overdose • Allergic reaction • Dental caries with reduced salivary production • CNS effects Missing information • Use in pregnancy and lactation • Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea • Safety in long term use beyond 24 weeks
1.5	awaiting approval	RMP updated further to update to SmPC and PIL Important Identified Risks • Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with cardiovascular disorders (including

		myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) • Aggravation of pyloric stenosis and paralytic ileus • Urinary retention • Constipation • Reduced bronchial secretions • Pneumonia • Using other medications with Glycopyrronium tablets (Interactions with other medicinal products) Important Potential Risks • Use in patients with ulcerative colitis • Drug-drug/food interaction leading to altered absorption and effect on other medicinal products • Risk in elderly patients • Risk in patients with uraemia • Risk in patients with intolerance to some sugars • Overdose • Allergic reaction • Use in patients with heart conditions (cardiac disorders) • Dental caries with reduced salivary production • CNS effects Missing information • Use in pregnancy and lactation • Off label use including use in children less than 3 years and use in patients with mild to

		moderate sialorrhea Safety in long term use beyond 24 weeks
1.6	awaiting approval	RMP updated further to update to SmPC and PIL and RFI Important Identified Risks • Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) • Aggravation of pyloric stenosis and paralytic ileus • Urinary retention • Constipation • Reduced bronchial secretions • Pneumonia • Using other medications with Glycopyrronium tablets (Interactions with other medicinal products) Important Potential Risks • Use in patients with ulcerative colitis • Drug-drug/food interaction leading to altered absorption and effect on other medicinal products • Risk in elderly patients • Risk in patients with uraemia • Risk in patients with intolerance to some sugars • Overdose

		• Allergic reaction • Use in patients with heart conditions (cardiac disorders) • Dental caries with reduced salivary production • CNS effects Missing information • Use in pregnancy and lactation • Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea • Safety in long term use beyond 24 weeks
1.7	awaiting approval	RMP updated further to update to SmPC and PIL and RFI Important Identified Risks • Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) • Aggravation of pyloric stenosis and paralytic ileus • Urinary retention • Constipation • Reduced bronchial secretions • Pneumonia • Using other medications with Glycopyrronium tablets (Interactions with other medicinal products) Important Potential Risks

		• Use in patients with ulcerative colitis • Drug-drug/food interaction leading to altered absorption and effect on other medicinal products • Risk in elderly patients • Risk in patients with uraemia • Risk in patients with intolerance to some sugars • Overdose • Allergic reaction • Use in patients with heart conditions (cardiac disorders) • Dental caries with reduced salivary production • CNS effects Missing information • Use in pregnancy and lactation • Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea Safety in long term use beyond 24 weeks
1.8	awaiting approval	RMP updated further to update to SmPC and PIL and RFI Important Identified Risks • Risk of overheating in patients with fever or in hot environment • Increase in heart rate; risk in patients with cardiovascular disorders (including myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) • Aggravation of pyloric

		stenosis and paralytic ileus • Urinary retention • Constipation • Reduced bronchial secretions • Pneumonia • Using other medications with Glycopyrronium tablets (Interactions with other medicinal products) Important Potential Risks • Use in patients with ulcerative colitis • Drug-drug/food interaction leading to altered absorption and effect on other medicinal products • Risk in elderly patients • Risk in patients with uraemia • Risk in patients with intolerance to some sugars • Overdose • Allergic reaction • Use in patients with heart conditions (cardiac disorders) • Dental caries with reduced salivary production • CNS effects Missing information • Use in pregnancy and lactation • Off label use including use in children less than 3 years and use in patients with mild to moderate sialorrhea Safety in long term use beyond 24 weeks