SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide 1mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1mg of Glycopyrronium bromide (or Glycopyrrolate).

Excipient with known effect
Contains lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

White to off-white, round, flat, beveled tablet (nominal diameter 5.5 mm) debossed with '1' on one side and a break line on the other side, without any visible defects.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients aged 3 years and older.

4.2 Posology and method of administration

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.

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

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.

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/1.73m^2) 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. The specific dose recommendations for each product must be followed to avoid overdose and anticholinergic side effects.

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).

4.3 Contraindications

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

In common with other antimuscarinics:
- Pregnancy and breast-feeding
- Angle-closure glaucoma
- Myasthenia gravis (large doses of quaternary ammonium compounds have been shown to antagonise end plate nicotinic receptors)
- History of intestinal obstruction
- Paralytic ileus
- Ulcerative colitis
- Pyloric stenosis
- Urinary retention
- Prostatic enlargement
- Severe renal impairment (eGFR <30 ml/min/1.73m^2), including those with end-stage renal disease requiring dialysis.
- Concomitant treatment with (see section 4.5):
  - potassium chloride solid oral dose products;
  - anticholinergics.

4.4 Special warnings and precautions for use

Anticholinergic effects
Anticholinergic effects such as urinary retention, constipation and overheating due to inhibition of sweating may be dose dependent and difficult to assess in a disabled child.

Monitoring by physicians and caregivers is required with adherence to the management instructions below:

Management of important anticholinergic side effects
The carer should stop treatment and seek advice from the prescriber in the event of:
- constipation
- urinary retention
- pneumonia
- allergic reaction
- pyrexia
- very hot weather
- changes in behaviour

After evaluating the event, the prescriber will decide if treatment should remain stopped or if this should continue at a lower dose.

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

Mild to moderate sialorrhoea
Due to the low potential benefit and the known adverse effect profile, glycopyrronium bromide tablets should not be given to children with mild to moderate sialorrhoea.

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

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

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

Respiratory

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

Central nervous system adverse events
Increased central nervous system effects have been reported in clinical trials including: irritability; drowsiness; restlessness; over activity; short attention span; frustration; mood changes; temper outbursts or explosive behaviour; excessive sensitivity; seriousness or sadness; frequent crying episodes; fearfulness. Behavioural changes should be monitored. As a consequence of its quaternary charge, glycopyrronium has limited ability to penetrate the blood brain barrier, although the extent of penetration is unknown. Caution should be exercised in patients with compromised blood brain barrier e.g. intraventricular shunt, brain tumour, encephalitis.

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

Growth and development
The effects of glycopyrronium on the reproductive system have not been investigated. Whilst clinical studies do not report any short or long-term effect of glycopyrronium on neurodevelopment or growth, no studies have been conducted to specifically address these issues.

Lactose
This medicine contains Lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Paediatric population
There are limited data available relating to interactions with other medicinal products in the paediatric age group. The following medicinal product interaction information is relevant to glycopyrronium.

Contraindications of concomitant use
Concomitant use of the following medicinal products is contraindicated (see section 4.3):

Potassium chloride solid oral dose: glycopyrronium may potentiate the risk of upper gastrointestinal injury associated with oral solid formulations of potassium chloride due to increased gastrointestinal transit time creating a high localized concentration of

potassium ions. An association with upper GI bleeding and small bowel ulceration, stenosis, perforation, and obstruction has been observed.

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

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

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

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

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

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women of childbearing potential must use effective contraception during treatment.

Pregnancy
There are no data on the use of glycopyrronium bromide tablets in pregnant women. The assessment of reproductive endpoints for glycopyrronium is limited (see section 5.3). Glycopyrronium is contraindicated in pregnancy (see section 4.3).

Breastfeeding
Safety in breast-feeding has not been established. Use whilst breast feeding is contraindicated (see section 4.3).

Fertility
There are no data on the effects of glycopyrronium bromide tablets on male or female fertility. Reproductive performance in rats given glycopyrronium shows a decrease in the rate of conception and in survival rate at weaning. There are insufficient data in the public domain to adequately assess effects on the reproductive system in young adults (see section 5.3).

4.7 Effects on ability to drive and use machines

Glycopyrronium bromide tablets may influence the ability to drive and use machines because it may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery, riding a bicycle, or performing hazardous work while taking this drug.

4.8 Undesirable effects

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

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

Tabulated list of adverse reactions
Adverse reactions reported in the literature for trials using glycopyrronium for sialorrhoea in the paediatric population (including 2 placebo-controlled trials, an uncontrolled safety study using glycopyrronium for a 6 month period, and 3 supportive studies with adverse event data in the target population) are listed by MedDRA system organ class (Table 3). Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the

corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon ≥1/1,000 to <1/100) rare; (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

List of Adverse Reaction Frequency

Adverse reaction	**Frequency category**
Infections and infestations	
Upper respiratory infection	Common
Pneumonia	Common
Urinary tract infection	Common
Psychiatric disorders	
Irritability	Very common
Agitation	Common
Drowsiness	Common
Restlessness	Not known
Overactivity	Not known
Short attention span	Not known
Frustration	Not known
Mood variable	Not known
Temper tantrum	Not known
Intermittent explosive disorder	Not known
Sensitivity, shyness, and social withdrawal disorder specific to childhood or adolescence	Not known
Feeling sad	Not known
Crying	Not known
Fear	Not known
Nervous system disorders	
Headache	Uncommon
Insomnia	Not known
Eye disorders	
Mydriasis	Uncommon
Nystagmus	Uncommon
Angle-closure glaucoma	Not known
Photophobia	Not known
Dry eyes	Not known
Cardiac disorders	
Flushing	Very common
Transient bradycardia	Not known
Respiratory, thoracic and mediastinal disorders	
Nasal congestion	Very common
Epistaxis	Common
Reduced bronchial secretions	Very common
Sinusitis	Not known
Gastrointestinal disorders	
Dry mouth	Very common
Constipation	Very common
Diarrhoea	Very common
Vomiting	Very common

Halitosis	Uncommon
Pseudo-obstruction	Uncommon
Gastrointestinal mobility disorder	Uncommon
Oesophageal candidiasis	Uncommon
Nausea	Not known
Skin and subcutaneous tissue disorders	
Rash	Common
Dryness of skin	Not known
Inhibition of sweating	Not known
Renal and urinary disorders	
Urinary retention	Very common
Urinary urgency	Not known
General disorders and administration site conditions	
Pyrexia	Common
Dehydration	Uncommon
Thirst in hot weather	Uncommon
Angioedema	Not known
Allergic reaction	Not known

Description of selected adverse reactions

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

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

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

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

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

Haematology and chemistry

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Overdose of glycopyrronium can result in anticholinergic syndrome, produced by the inhibition of cholinergic neurotransmission at muscarinic receptor sites. Clinical manifestations are caused by CNS effects, peripheral nervous system effects, or both. Common manifestations include flushing, dry skin and mucous membranes, mydriasis with loss of accommodation, altered mental status and fever. Additional manifestations include sinus tachycardia, decreased bowel sounds, functional ileus, urinary retention, hypertension, tremulousness and myoclonic jerking.

Management
Patients presenting with anticholinergic toxicity should be transported to the nearest emergency facility with advanced life support capabilities. Pre-hospital gastrointestinal decontamination with activated charcoal is not recommended because of the potential for somnolence and seizures and the resulting risk of pulmonary aspiration. At hospital, activated charcoal can be administered if the patient's airways can be adequately protected. Physostigmine salicylate is recommended when tachydysrhythmia with subsequent hemodynamic compromise, intractable seizure, severe agitation or psychosis is present.

Patients and/or parents/caregivers should be counselled to ensure an accurate dose is given each time, in order to prevent the harmful consequences of anticholinergic reactions of glycopyrronium seen with dosing errors or overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products for functional gastrointestinal disorders, synthetic anticholinergics, ATC code: A03AB02.

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

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

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

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

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

Placebo controlled efficacy data includes patients with a treatment duration of 8 weeks. There is no placebo or comparator controlled data beyond 8 weeks.

Zeller *et al* 2012 evaluated the efficacy of glycopyrronium bromide oral solution (1 mg/5 mL) in managing problem drooling associated with cerebral palsy and other neurologic conditions. Thirty-eight patients aged 3–23 years weighing at least 27 lb (12.2 kg) with severe drooling (clothing damp 5–7 days/week) were randomized to eight-weeks treatment with glycopyrronium (n = 20), 20-100 µg/kg (not exceeding 3 mg in total) three times a day, or matching placebo (n = 18). The first four weeks were an individual titration period in fixed steps depending on response followed by 4-weeks maintenance treatment. Primary efficacy endpoint was responder rate, defined as percentage showing ≥3-point improvement on the modified Teacher's Drooling Scale (mTDS). The primary analysis population was revised to only comprise patients with an age of 3 -16 years which rendered 19 patients in the glycopyrrolate oral solution group and 17 in the placebo group. Responder rate was defined as at least a 3-point improvement in modified Teacher's Drooling Scale (mTDS).

Responder rate at week 8	**At least a 3-point improvement in mTDS**	**Mean improvements in mTDS**
Glycopyrronium	14 of 19 patients (73.7%)	3.94 points (SD: 1.95; 95%; CI: 2.97 – 4.91)
Placebo	3 of 17 patients (17.6%)	0.71 points (SD: 2.14; 95% CI: –0.43 – 1.84)
p value	p = 0.0011	p <0.0001

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

The safety and efficacy of glycopyrronium have been studied in an open labelled study with no control group over a 24-week period in children aged 3 to 18 years. At the week 24/exit visit, 52.3% (95% confidence interval 43.7–60.9) of patients (n=130) had an at least three-point decrease in mTDS from baseline and were classified as responders to treatment with oral glycopyrrolate solution. The adverse event profile was consistent with the one seen with anticholinergics (see section 4.4 and 4.8).

5.2 Pharmacokinetic properties

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

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

In adults, distribution of glycopyrronium was rapid following a single 6 µg/kg i.v. dose; distribution half-life was 2.2 ± 1.3 minutes. Following administration of ^{3}H-labelled glycopyrronium more than 90% of the radiolabel disappeared from the plasma in 5 minutes, and almost 100% within 30 minutes, reflecting rapid distribution. Analyses of population pharmacokinetic data from healthy adults and children with cerebral palsy-associated chronic moderate to severe drooling who received glycopyrronium (route of administration and dosages not specified) did not demonstrate linear pharmacokinetics of the medicinal product.

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

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

In a study in healthy adults, a 2000 µg single dose of glycopyrronium bromide resulted in an AUC of 2.39 µg.h/L (fasted). An AUC0-6 h of 8.64 µg.h/L was observed after 6 µg/kg i.v. glycopyrronium.

Based upon theoretical physicochemical considerations, the quaternary ammonium compound glycopyrronium would be expected to have low central bioavailability; no glycopyrronium was detectable in the CSF of anaesthetised surgical patients or patients undergoing caesarean section following a 6 – 8 µg/kg i.v. dose. In the paediatric

population 5 µg/kg i.v. glycopyrronium has low central bioavailability, except in the case where the blood brain barrier has been compromised (e.g. a shunt infection).

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

The elimination half-life of glycopyrronium appears to be dependent on route of administration being 0.83 ± 0.27 hours after i.v. administration, 75 minutes after i.m. administration and in the region of 2.5 - 4 h after oral (solution) administration, though again this was highly variable. That the latter two half-lives, and especially that for oral administration, are longer than for i.v. administration probably reflects the complex absorption and distribution of glycopyrronium by each route. It is possibl e that prolonged absorption after oral administration translates into elimination being faster than absorption (known as flip-flop kinetics, characterized by Ka < Ke).

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

A mean increase in total systemic exposure (AUC_{last}) of up to 1.4-fold was seen in adult subjects with mild and moderate renal impairment (GFR ≥30ml/min/1.73m^2) and up to 2.2-fold in subjects with severe renal impairment or end stage renal disease (estimated GFR <30ml/min/1.73m^2). A 30% dose reduction (see section 4.2) is required for patients with mild to moderate renal impairment. Glycopyrronium is contraindicated in patients with severe renal impairment.

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

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

Co-administration with food results in a marked decrease in systemic glycopyrronium exposure (see section 4.2.).
Different formulations of glycopyrronium differ in bioavailability and should not be regarded as interchangeable (see section 4.2).

5.3 Preclinical safety data

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

The single-dose toxicity of glycopyrronium has been tested in a range of investigations, although only limited experimental details are available. Upon oral administration, high LD50 values of 550 mg/kg in mice and above 1000 mg/kg in rats were reported. In rats at higher doses (1500-2000 mg/kg) signs of toxicity were tremors, clonic and tonic convulsions and laboured breathing were observed prior to death, resulting from respiratory failure.

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Anhydrous calcium hydrogen phosphate
Magnesium stearate
Povidone K-30
Sodium starch glycolate

6.2 Incompatibilities

None known

6.3 Shelf life

Unopened bottle: 3 years
Do not use after five weeks of first opening.

Blister: 3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in original container.

6.5 Nature and contents of container

HDPE bottle with screw-cap.
Pack size: 100 tablets

Alu-Alu blister packs of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 100 and 112 tablets (with or without calendar pack).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 30684/0125

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