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 indirectly reducing the rate of salivation.

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

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

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

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

Responder rate at	At least a 3-point	Mean improvements in mTDS

week 8	improvement in mTDS	
Glycopyrronium	14 of 19 patients (73.7%)	3.94 points (SD: 1.95; 95%; CI: 2.97–4.91)
Placebo	3 of 17 patients (17.6%)	0.71 points (SD: 2.14; 95% CI: –0.43–1.84)
p value	p = 0.0011	p <0.0001

In addition, 84% of physicians and 100% of parents/caregivers regarded glycopyrrolate as worthwhile compared with 41% and 56%, respectively, for placebo ($p \leq 0.014$). 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 $AUC_{0-6\,h}$ of 8.64 µg.h/L was observed after 6 µg/kg i.v. glycopyrronium.

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

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

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

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

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

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

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

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

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

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 LD_{50} values of 550 mg/kg in mice and above 1000 mg/kg in rats were reported. In rats at higher doses (1500-2000 mg/kg) signs of toxicity were tremors, clonic and tonic convulsions and laboured breathing were observed prior to death, resulting from respiratory failure.

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate

Lactose anhydrous

Povidone

Sodium starch glycolate

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

After first opening: 3 months

6.4 Special precautions for storage

None

6.5 Nature and contents of container

Tablets are 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.

6.6 Special precautions for disposal

No Special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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UB8 3HD, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 44710/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

17/12/2020