SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sialanar 320 micrograms /ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 400 micrograms of glycopyrronium bromide equivalent to 320 micrograms of glycopyrronium.

Excipient(s) with known effect

Each ml contains 2.3 mg sodium benzoate (E211).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

4.2 Posology and method of administration

Sialanar should be prescribed by physicians experienced in the treatment of paediatric patients with neurological disorders.

Posology

Due to the lack of long term safety data, Sialanar is recommended for short -term intermittent use (see section 4.4).

Paediatric population – children and adolescents aged 3 years and older
The dosing schedule for glycopyrronium is based on the weight of the child, starting with approximately 12.8 micrograms/kg per dose (equivalent to 16 micrograms/kg per dose glycopyrronium bromide), three times per day and increasing by the doses shown in Table 1 below, every 7 days. Dose titration should be continued until efficacy is balanced with undesirable effects and amended up or down as appropriate, to a maximum individual dose of 64 micrograms/kg body weight glycopyrronium or 6 ml (1.9 mg glycopyrronium, equivalent to 2.4 mg glycopyrronium bromide) three times a day, whichever is less. Dose titrations should be conducted in discussion with the carer to assess both efficacy and undesirable effects until an acceptable maintenance dose is achieved.

Undesirable effects may be minimised by using the lowest effective dose necessary to control symptoms. It is important that the carer checks the dose volume in the syringe before administration. The maximum volume of the highest dose is 6 ml. In the event of a known anticholinergic adverse reaction occurring when the dose is increased, the dose should be reduced to the previous lower dose and the event monitored (see section 4.4). If the event does not resolve treatment should be discontinued. In the event of constipation, urinary retention or pneumonia (see section 4.8), treatment should be stopped and the prescribing physician contacted.
Younger children may be more susceptible to adverse reactions and this should be borne in mind when any 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.

The Table 1 shows the dose in ml of solution to be given for each weight range at each dosing increase.

Table 1. Dosing table for children and adolescents with normal renal function

Weight	**Dose level 1**	**Dose level 2**	**Dose level 3**	**Dose level 4**	**Dose level 5**
Kg	**(~12.8µg/kg)**[1]	**(~25.6µg/kg)**[1]	**(~38.4µg/kg)**[1]	**(~51.2µg/kg)**[1]	**(~64µg/kg)**[1]
	ml	**ml**	**ml**	**ml**	**ml**
13-17	0.6	1.2	1.8	2.4	3*
18-22	0.8	1.6	2.4	3.2	4*
23-27	1	2	3	4	5*
28-32	1.2	2.4	3.6	4.8	6*
33-37	1.4	2.8	4.2	5.6	6*
38-42	1.6	3.2	4.8	6*	6
43-47	1.8	3.6	5.4	6*	6
≥48	2	4	6*	6	6

[1] refers to µg/kg glycopyrronium
*Maximum individual dose in this weight range

Special populations

Paediatric population (children aged < 3 years)
The safety and efficacy of glycopyrronium bromide in children aged from birth to < 3 years has not been established. No data are available.

Adult population
Sialanar is indicated for the paediatric population only. There is limited clinical trial evidence on the use of glycopyrronium in the adult population with pathological drooling.

Elderly
Sialanar is indicated for the paediatric population only. 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 Sialanar should not be used in patients over the age of 65 years.

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.

Renal impairment
Doses should be reduced by 30% in patients with mild to moderate renal impairment (eGFR <90 - ≥30 ml/min/1.73m^2) (see Table 2). This medicinal product is contraindicated in patients with severe renal impairment (eGFR <30 ml/min/1.73m^2), including those with end-stage renal disease requiring dialysis (see section 4.3).

Table 2. Dosing table for children and adolescents with mild to moderate renal impairment

Weight	**Dose level 1**	**Dose level 2**	**Dose level 3**	**Dose level 4**	**Dose level 5**
Kg	**(~8.8µg/kg)** [1]	**(~17.6µg/kg)**[1]	**(~27.2µg/kg)**[1]	**(~36µg/kg)**[1]	**(~44.8µg/kg)**[1]
	ml	**ml**	**ml**	**ml**	**ml**
13-17	0.4	0.8	1.2	1.7	2.1*
18-22	0.6	1.1	1.7	2.2	2.8*
23-27	0.7	1.4	2.1	2.8	3.5*
28-32	0.8	1.7	2.5	3.4	4.2*
33-37	1	2	2.9	3.9	4.2*
38-42	1.1	2.2	3.4	4.2*	4.2
43-47	1.2	2.5	3.8	4.2*	4.2
≥48	1.4	2.8	4.2*	4.2	4.2

[1] refers to µg/kg glycopyrronium
*Maximum individual dose in this weight range

Method of administration

For oral use only.

Co-administration with food results in a marked decrease in systemic medicinal product exposure (see section 5.2). 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 child's specific needs determine that co-administration with food is required, dosing of the medicinal product should be consistently performed during food intake.

Insert the syringe adaptor into the neck of the bottle. Insert the end of the oral syringe into the syringe adaptor and ensure it is secure. Turn the bottle upside down. Gently pull down the plunger to the correct level (see Tables 1 and 2 for the correct dose). Turn the bottle upright. Remove the oral syringe. Place the oral syringe inside the child's mouth and press the plunger slowly to gently release the medicinal product. If the child is given the medicinal product through a feeding tube, flush the tube with 10 ml of water after you have given the medicinal product.

The oral syringe should be gently washed with warm water and allowed to dry after each use (i.e. three times per day). Do not use a dishwasher.

4.3 Contraindications

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

Pregnancy and breast-feeding.

Glaucoma.

Urinary retention.

Severe renal impairment (eGFR <30 ml/min/1.73m^2), including those with end-stage renal disease requiring dialysis.

History of intestinal obstruction, ulcerative colitis, paralytic ileus, pyloric stenosis and myasthenia gravis.

Concomitant treatment with potassium chloride solid oral dose and anticholinergics (see section 4.5).

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:

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 (see section 4.2).

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 likelihood of benefit and the known adverse effect profile, Sialanar 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 (see section 4.8). The carer should be advised to measure the pulse rate if the child seems unwell and report very fast or very slow heart rate.

Gastro-intestinal disorders

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

Dental disorders

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 disorders

Glycopyrronium can cause thickening of secretions, which may increase the risk of respiratory infection and pneumonia (see section 4.8). Glycopyrronium should be discontinued if pneumonia is present.

Central nervous system (CNS) adverse reactions

Increased CNS 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 and fearfulness (see section 4.8). 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 children with compromised blood brain barrier, e.g. intraventricular shunt, brain tumour, encephalitis.

Children below the age of 3 years

Sialanar 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

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per maximum dose, that is to say essentially ‘sodium free’.

Sodium benzoate
This medicinal product contains 2.3 mg sodium benzoate (E211) in each ml.

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 (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 gastrointestinal 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

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

Topiramate
Glycopyrronium may potentiate the effects of oligohidrosis and hyperthermia associated with the use of topiramate, particularly in pediatric patients.

Sedating antihistamines
Sedating antihistamines may have additive anticholinergic effects. A reduction in anticholinergic and/or antihistamine dose 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
Tricyclic antidepressants and MAOIs may have additive anticholinergic effects. A reduction in anticholinergic and/or tricyclic antidepressants and MAOIs dose may be necessary.

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

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

Other

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Effective contraception should be considered prior to treating women of childbearing age, where appropriate.

Pregnancy

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

Breast-feeding

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

Fertility

There are no data on the effects of Sialanar 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

Sialanar has moderate influence on the ability to drive and use machines. The anticholinergic effects of glycopyrronium may cause blurred vision, dizziness and other effects that may impair a patient's ability to perform skilled tasks such as driving, riding a bicycle and using machines. The undesirable effects are increased with increasing dose.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions are common with glycopyrronium due to its known pharmacodynamic anticholinergic effects. The most common adverse reactions are dry mouth (11%), constipation (20%), diarrhoea (18%), vomiting (18%), urinary retention (15%), flushing (11%) and nasal congestion (11%).
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 reaction data in the target population) are listed by MedDRA system organ class (Table 3). Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3. List of adverse reactions

Adverse reactions	**Frequency category**
Infections and infestations	
Upper respiratory tract 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

Adverse reactions	**Frequency category**
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
Oesophageal candidiasis	Uncommon
Gastrointestinal motility disorder	Uncommon
Pseudo-obstruction	Uncommon
Nausea	Not known
Skin and subcutaneous tissue disorders	
Rash	Common
Dryness of the 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 stopped until the urinary retention resolves.

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

Constipation
Constipation is a known adverse reaction associated with anticholinergic medicinal products (30%). Glycopyrronium treatment should be stopped 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 (see section 4.4).

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 (see section 4.4).

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:

Yellow Card Scheme

Website: 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 acurate 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, quaternary ammonium compounds, ATC code: A03AB02.

Mechanism of action

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

Pharmacodynamic effects

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.

Clinical efficacy and safety

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 randomised 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 safety profile was consistent with the one seen with anticholinergics (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Mean absolute oral bioavailability of glycopyrronium comparing a single 50 μg/kg oral dose and a single 5 μg/kg intravenous 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.

Distribution

In adults, distribution of glycopyrronium was rapid following a single 6 μg/kg intravenous 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 doses 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 intravenous 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 (V_{ss}) and clearance (Cl) have been observed in children between 1 and 3 years of age, leading to a statistically significant shorter elimination half-life ($t_{½, z}$) than that observed in younger (<1 year of age; p = 0.037) or older (>3 years of age; p = 0.042) groups.

In a study in healthy adults, a 2000 µg single dose of glycopyrronium bromide resulted in an AUC of 2.39 µg.h/L (fasted). An $AUC_{0\text{-}6\ h}$ of 8.64 µg.h/L was observed after 6 µg/kg intravenous 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 intravenous dose. In the paediatric population 5 µg/kg intravenous glycopyrronium has low central bioavailability, except in the case where the blood brain barrier has been compromised (e.g. a shunt infection).

Elimination

The primary route of elimination of glycopyrronium is via renal excretion, mainly as unchanged medicinal product. Approximately 65% of an intravenous 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 intravenous administration, 75 minutes after intramuscular 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 intravenous 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 intravenous 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 Table 2) is required for patients with mild to moderate renal impairment. Glycopyrronium is contraindicated in patients with severe renal impairment.

Other

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

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

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

5.3 Preclinical safety data

Non-clinical data, including genotoxicity or carcinogenicity studies have not been performed for Sialanar.
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 1,000 mg/kg in rats were reported. In rats at higher doses (1500-2000 mg/kg) 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

Sodium benzoate (E211)
Raspberry flavouring (containing propylene glycol E1520)
Sucralose (E955)
Citric acid (E330)
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

2 months after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber coloured glass bottle with a high density polyethylene tamper evident child resistant closure with expanded low density polyethylene liner. The bottle contains 60 ml or 250 ml of oral solution.

Pack size of one bottle, one 8 ml low density polyethylene oral syringe (0.1 ml graduations) and one syringe adaptor.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Proveca Pharma Limited
2 Dublin Landings
North Wall Quay
Dublin 1
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 42588/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/12/2021

10 DATE OF REVISION OF THE TEXT

16/01/2023