Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rybrila 160 micrograms/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml oral solution contains 200 micrograms of glycopyrronium bromide equivalent to 160 micrograms of glycopyrronium.

Excipient(s) with known effect
Sorbitol (E420)
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Rybrila is a clear, colourless, strawberry flavoured liquid. The oral solution has a pH between 3.5 and 4.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rybrila is indicated for the 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

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

Posology

Rybrila is recommended for short-term intermittent use (see section 4.4 and 5.1).
The dosage must be measured and administered with the graduated oral syringe included in the pack.
The dosing schedule for Rybrila is based on the weight of the child with the initial dosing of 16 micrograms/kg per dose (equivalent to 20 micrograms/kg per dose glycopyrronium bromide) to be given orally three times daily and titrate in increments of 16 micrograms/kg every 5-7 days based on therapeutic response and adverse reactions (see section 4.4 *Anticholinergic effects)*. 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 80 micrograms/kg body weight glycopyrronium or 15 ml 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. 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. In the event of a known anticholinergic adverse event (AE) occurring when the dose is increased, the dose should be reduced to the previous lower dose and the event monitored. If the AE does not resolve treatment should be discontinued.
Younger children may be more susceptible to adverse events and this should be kept in mind when dose adjustments are carried out.

Table 1: Dosing table 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	**(~16 µg/kg)***	**(~32 µg/kg)***		**(~48µg/kg)***	**(~64 µg/kg)***	**(~80 µg/kg)***
13-17	1.5 ml		3 ml	4.5 ml	6 ml	7.5 ml

18-22	2 ml	4 ml	6 ml	8 ml	10 ml
23-27	2.5 ml	5 ml	7.5 ml	10 ml	12.5 ml
28-32	3 ml	6 ml	9 ml	12 ml	15 ml
33-37	3.5 ml	7 ml	10.5 ml	14 ml	15 ml
38-42	4 ml	8 ml	12 ml	15 ml	15 ml
43-47	4.5 ml	9 ml	13.5 ml	15 ml	15 ml
≥48	5 ml	10 ml	15 ml	15 ml	15 ml

**refers to micrograms/kg Glycopyrronium*

Paediatric population – children younger than 3 years

Rybrila is not recommended for use in children younger than 3 years.

Adult population

There is limited clinical evidence on the use of glycopyrronium in the adult population with pathological drooling.

Elderlypopulation

Rybrila 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 Rybrila should not be used in patients over the age of 65 years.

Hepatic Impairment

Clinical studies have not been evaluated in patients with hepatic impairment. glycopyrronium is eliminated largely from the renal excretion and hepatic impairment is not thought to result in an increase in a systemic exposure of glycopyrronium.

Renal impairment

Elimination of glycopyrronium is severely impaired in patients with mild to moderate renal impairment therefore doses should be reduced by 30% (see Table 2). This medicine is contraindicated in severe renal impairment (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	**(~11.2 µg/kg)***	**(~22.4 µg/kg)***		**(~33.6µg/kg)***	**(~44.8 µg/kg)***	**(~56 µg/kg)***
13-17	1.1 ml		2.1 ml	3.2 ml	4.2 ml	5.3 ml[1]
18-22	1.4 ml		2.8 ml	4.2 ml	5.6 ml	7.0 ml [1]
23-27	1.8 ml		3.5 ml	5.3 ml	7.0 ml	8.8 ml[1]
28-32	2.1 ml		4.2 ml	6.3 ml	8.4 ml	10.5 ml[1]
33-37	2.5 ml		4.9 ml	7.4 ml	9.8 ml	10.5 ml[1]
38-42	2.8 ml		5.6 ml	8.4 ml	10.5 ml[1]	10.5 ml
43-47	3.2 ml		6.3 ml	9.5 ml	10.5 ml[1]	10.5 ml
≥48	3.5 ml		7.0 ml	10.5 ml	10.5 ml	10.5 ml

*refers to micrograms/kg Glycopyrronium

[1]Maximum individual dose in this weight range

Administration with food

High fat food should be avoided. The presence of high fat food reduces the oral bioavailability of glycopyrronium if given shortly after a meal. Therefore, it should be given at least one hour before or two hours after meals. If 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).

Method of administration

Other glycopyrronium products with different strengths are available. Switching between these products without proper dose adjustments may lead to overdose and, in turn, anticholinergic toxicity (see section 4.8 and 4.9).

For oral use and use with nasogastric and or PEG tubes.

The correct quantity of Rybrila should be measured and administered using the oral syringe included in the pack.

Nasogastric or PEG feeding tubes, if used, should be flushed with 20 ml of water immediately after dosing. See Section 6.6 for instructions for use.

Instructions for use
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 Table 1 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 Rybrila is given through a feeding tube, flush the tube with 20 ml of water after administering the medicinal product.

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:

- Angle-closure glaucoma
- Myasthenia gravis (large doses of quaternary ammonium compounds have been shown to antagonise end plate nicotinic receptors);
- Pyloric stenosis;
- Paralytic ileus;
- Urinary retention;
- Severe renal impairment (eGFR <30 ml/min/1.73m^2, including those with end-stage renal disease requiring dialysis (see section 5.2);
- Intestinal obstruction;
- Potassium chloride solid oral dose products (see section 4.5);
- Anticholinergic medicines (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 are dose dependent. 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.

Rybrila should be used with caution in gastro-oesophageal reflux disease, ulcerative colitis, pre-existing constipation, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) because of the increase in heart rate produced by its administration, coronary artery disease and cardiac arrhythmias.

Due to the potential change to normal heart rhythm, Rybrila should be used with caution in patients receiving inhalation anaesthesia.

Diarrhoea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful.

Because Rybrila inhibits sweating, patients with increased temperature should be observed closely. In the presence of a high environmental temperature, heat prostration (fever and heat stroke due to decreased sweating) can occur with use of this medicinal product.

Because of prolongation of renal elimination, repeated or large doses of Rybrila should be avoided in patients with uraemia.

Patients with rare hereditary problems of fructose intolerance should not take this medicine. This is due to the presence of sorbitol (E420) in this medicine.

Rybrila contains sodium propyl parahydroxybenzoate (E217) and sodium methyl parahydroxybenzoate (E219). These may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol sodium (23 mg) per maximum dose, i.e. essentially is 'sodium free'.

Paediatric population – children younger than 3 years
Rybrila is not recommended for use in children younger than 3 years of age.

Lack of long-term safety data
Safety data are not available beyond 24 weeks treatment duration. Given the limited long-term safety data available and the uncertainties around the long term use of the product, the 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, Rybrila should not be given to children with mild to moderate sialorrhoea.

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.

CNS adverse events
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. 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

- Potassium chloride solid oral dose products: 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.

- Anticholinergic medicines: 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 including dose adjustment

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.

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;

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

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

Pregnancy
There is limited amount of data (less than 300 pregnancy outcomes) from the use of glycopyrronium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Rybrila during pregnancy.

Breastfeeding
Available toxicological data in animals have shown excretion of glycopyrronium and its metabolites in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue from Rybrilatherapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effects of Rybrila on male or female fertility. Animal data do not indicate an effect of glycopyrronium on male or female fertility at clinically relevant exposures.

4.7 Effects on ability to drive and use machines

Rybrila 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, or performing hazardous work while taking this medicinal product.

4.8 Undesirable effects

Rybrila may produce the following effects, which are extensions of its fundamental pharmacological actions: dry mouth, diminished gastrointestinal motility, difficulty in micturition, increased body temperature and inhibition of sweating.

Side-effects of antimuscarinics include difficulty swallowing, difficulty talking, thirst, constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, flushing, and dryness of the skin.

Other side-effects that occur less frequently include confusion (particularly in the elderly), nausea, vomiting, drowsiness, dizziness andangle-closure glaucoma.

Summary of the safety profile
The highest incidence of adverse reactions associated with glycopyrronium therapy is related to its anticholinergic properties[1] i.e. dry mouth (13%), constipation (16%), diarrhoea (9.4%), nasal congestion (8.4%), vomiting (11.4%), urinary retention (5.4%) etc.
Pulmonary undesirable effects including upper respiratory infection and pneumonia have been reported (See Section 4.4).
There is no data on the long-term use of the product. (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions associated with glycopyrronium obtained from published studies[1] are tabulated below according to the following convention: Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Unknown (cannot be estimated from the available data)

System Organ Class	Frequency			
	Very Common	**Common**	**Uncommon**	**Unknown**
Immune system disorder			allergic reaction	
Nervous system disorder			seizure (worsening), dizziness, insomnia	headache, somnolence, drowsiness
Gastrointestinal disorder	dry mouth, constipation, diarrhoea, vomiting		pseudo-obstruction, gastrointestinal mobility disorder, eosophageal candidiasis, breath odour	nausea
Infections and infestations		pneumonia		upper respiratory infection, otitis media, streptoccocal pharyngitis, urinary tract infection
Psychiatric disorder	behavioural changes[2]			
Eye disorder			nystagmus	mydriasis, blurred vision, angle-closure glaucoma, photophobia, dry eyes
Cardiac disorder	flushing			angioedema, transient bradycardia
Respiratory, thoracic and mediastinal disorders	nasal congestion, reduced bronchial secretions			epistaxis, sinusitis
Skin and subcutaneous			hives	rash, skin dryness, sweat inhibition

tissue disorder				
Renal and urinary disorders		urinary retention	urinary urgency	
General disorders and administration site conditions		pyrexia	dehydration, thirst	

[1] Frequency categories are assigned from the pooled datafrom the following published studies: double blinded placebo controlled trials Mier et al. and Zeller et al. 2012a, one retrospective review Bachrach et al., and three one open –label studies Zeller et al 2012b, Stern and Blasco et al. with a total of 297 patients exposed to glycopyrronium.
[2] Behavioural changes include agitation, drowsiness, restlessness, overactivity, short attention span, frustration, irritability, mood changes, temper outbursts, explosive behaviour, excessive sensitivity, seriousness, sadness, frequent crying, fearfulness.

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Since glycopyrronium is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature. Theoretically, with overdosage, a curare-like action may occur, i.e. neuro-muscular blockade leading to muscular weakness and possible paralysis. Furthermore, the likelihood of experiencing anticholinergic side effects is increased.

Treatment of overdose is symptomatic and supportive.

- To guard against further absorption of the drug, use gastric lavage, cathartics and/or enemas.
- To combat peripheral anticholinergic effects (residual mydriasis, dry mouth, etc.), utilise a quaternary ammonium anticholinesterase, such as neostigmine. Proportionately smaller doses should be used in children.
- To combat hypotension, use pressor amines (norepinephrine, metaraminol) i.v. and supportive care.

To combat respiratory depression, administer oxygen; utilise a respiratory stimulant such as Doxapram hydrochloride i.v. and artificial respiration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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.

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 (160 micrograms/ 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 glycopyrronium 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 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 glycopyrronium as worthwhile compared with 41% and 56%, respectively, for placebo (p≤0.014). Most frequently reported treatment-emergent adverse events (glycopyrronium 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 glycopyrronium solution. The adverse event profile was consistent with the one seen with anticholinergics (see section 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

Glycopyrronium is poorly absorbed from the gastrointestinal tract. Oral glycopyrronium has low oral bioavailability; a mean of approximately 3% is found in plasma.

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

Oral glycopyrronium produces low plasma concentrations (C_{max} 0.318 ± 0.190 ng/ml) lasting up to 12 hours.

Food effect data indicate that the mean C_{max} under fed high fat meal conditions is about 74% lower than the C_{max} observed under fasting conditions (see section 4.4).

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.

Distribution
In adults, distribution of glycopyrronium was rapid following a single 6 micrograms/kg i.v. dose; distribution half-life was 2.2 ± 1.3 minutes. Following administration of 3H-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 micrograms/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 micrograms single dose of glycopyrronium resulted in an AUC of 2.39 micrograms.h/L (fasted). An AUC0-6 h of 8.64 micrograms.h/L was observed after 6 micrograms/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 micrograms/kg i.v. dose. In the paediatric population 5 micrograms/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).

Biotransformation

In adult patients who underwent surgery for cholelithiasis and were given a single IV dose of tritiated glycopyrronium, approximately 85% of total radioactivity was excreted in urine and < 5% was present in T-tube drainage of bile. In both urine and bile, > 80% of the radioactivity corresponded to unchanged drug. These data suggest a small proportion of i.v. glycopyrronium bromide is excreted as one or more metabolites.

Elimination

A study using intravenous ^{3}H-glycopyrronium in humans showed the disappearance of more than 90% from the serum in 5 minutes and almost 100% in 30 minutes. Urinary radioactivity was highest in the first 3 hours and 85% was excreted in the urine within 48 hours. Paper chromatography showed 80% of the radioactivity in bile and urine corresponding to unchanged glycopyrronium. Following oral administration to mice, 7.6% was excreted in the urine and about 79% in the faeces.

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 (AUClast) 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 is required for patients with mild to moderate renal impairment. Glycopyrronium is contraindicated in patients with severe renal 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.

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

Glycopyrronium penetrates the blood-brain barrier poorly. Glycopyrronium crosses the placenta to a limited extent; and is not known whether it is distributed into milk.

5.3 Preclinical safety data

Non-clinical studies, have not been performed for Glycopyrronium oral solution.

Limited non-clinical literature data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose, genotoxicity, carcinogenicity or reproductive and developmental toxicity .

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.

No studies in juvenile animals have been performed with glycopyrronium. Risks for the paediatric population cannot be excluded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol Sorbitol (E420)
Sodium methyl parahydroxybenzoate (E219) Sodium propyl parahydroxybenzoate (E217) Citric acid monohydrate (E330)
Trisodium citrate dihydrate (E331)
Purified water
Strawberry flavour:
Flavouring substance Maltodextrin (maize) Acacia (E414) Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once opened, the product may be stored for up to 28 days at a maximum of 25°C. Other in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C.
Store in the original bottle. Keep bottle in the original carton in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

150 ml amber type III glass bottle with a tamper evident child resistant HDPE/PP screw cap.
Each 150 ml bottle is provided in a cardboard carton with a 15 ml graduated LDPE oral syringe and a PE syringe adaptor to allow the correct dose to be measured.

Rybrila is also available in multipacks of 2 x 150 ml, 3 x 150 ml, 4 x 150 ml, and 5 x 150 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If Rybrila is given through a feeding tube, flush the tube with 20 ml of water after administering the medicinal product.
No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport
D Tower 11th floor
1118BJ Schiphol
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22701/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd July 2021

10 DATE OF REVISION OF THE TEXT

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