SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rybrila

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of oral solution contains 0.16mg of Glycopyrronium (as bromide)

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.

Patient safety information card:

The marketing of Rybila is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

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

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 syringe included in the pack.

The dosing schedule for Rybrila 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.

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	0.3 mg	1.5 ml	0.6 mg	3 ml	0.9 mg	4.5 ml	1.2 mg	6 ml	1.5 mg	7.5 ml
18-22	0.4 mg	2 ml	0.8 mg	4 ml	1.2 mg	6 ml	1.6 mg	8 ml	2.0 mg	10 ml
23-27	0.5 mg	2.5 ml	1.0 mg	5 ml	1.5 mg	7.5 ml	2.0 mg	10 ml	2.5 mg	12.5 ml
28-32	0.6 mg	3 ml	1.2 mg	6 ml	1.8 mg	9 ml	2.4 mg	12 ml	3.0 mg	15 ml
33-37	0.7 mg	3.5 ml	1.4 mg	7 ml	2.1 mg	10.5 ml	2.8 mg	14 ml	3.0 mg	15 ml
38-42	0.8 mg	4 ml	1.6 mg	8 ml	2.4 mg	12 ml	3.0 mg	15 ml	3.0 mg	15 ml
43-47	0.9 mg	4.5 ml	1.8 mg	9 ml	2.7 mg	13.5 ml	3.0 mg	15 ml	3.0 mg	15 ml
≥48	1.0 mg	5 ml	2.0 mg	10 ml	3.0 mg	15 ml	3.0 mg	15 ml	3.0 mg	15 ml

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

The medicinal product will be prescribed by physicians specialized in the treatment of pediatric patients with neurological disorders.

Hepatic Impairment

Clinical studies have not been evaluated in patients with hepatic impairment. Glycopyrrolate 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 glycopyrrolate is severely impaired in patients with renal failure therefore reduction in doses should be considered.

High fat food should be avoided. The presence of high fat food reduces the oral bioavailability of Rybrila 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

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

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

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

4.3 Contraindications

- Hypersensitivity to the active substance 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
- Prostatic enlargement
- Urinary retention
- Severe renal impairment (eGFR <30 ml/min/1.73m^2, including those with end-stage renal disease requiring dialysis
- Intestinal obstruction
- Pregnancy and breast-feeding.
- Potassium chloride solid oral dose products
- Anticholinergic medicines

4.4 Special warnings and precautions for use

Rybrila oral solution 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.

As 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 Rybrila oral solution.

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 ’.

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

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.

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
.

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 eg. Intraventicular 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

Class interactions

Many drugs have antimuscarinic effects; concomitant use of two or more of such drugs can increase side-effects such as dry mouth, urine retention and constipation. Concomitant use can also lead to confusion in the elderly. The Rybrila dosage may need to be decreased in patients receiving two or more antimuscarinic drugs concomitantly.

Increased antimuscarinic side-effects: amantadine; tricyclic antidepressants; antihistamines; clozapine; disopyramide; MAOIs; nefopam; memantine; phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations)

Possibly increased antimuscarinic side-effects: tricyclic (related) antidepressants

Anticholinergic agents may delay absorption of other medication given concomitantly.

Concurrent administration of anticholinergics and corticosteroids may result in increased intraocular pressure.

Concurrent use with slow-dissolving tablets of digoxin, atenolol or metformin may result in increased serum levels of these medicines.

Concurrent use with parasympathomimetics may antagonise the effect.

Specific interactions

Domperidone/Metoclopramide: antagonism of effect on gastro-intestinal activity

Levodopa: absorption of levodopa possibly reduced

Haloperidol: effects of haloperidol possibly reduced

Nitrates: possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)

Topiramate and *zonisamide*: enhanced effect (reduction of sweating)

Inhaled anaesthetics: potential change to normal heart rhythm

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of childbearing potential have to use effective contraception during the treatment.

Pregnancy

There are no data on the use of Rybrila Oral solution 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 Rybrila oral solution 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

Rybrila oral solution 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 drug.

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 and angle-closure glaucoma.

Summary of the safety profile

The highest incidence of adverse reactions associated with Rybrila 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. The incidence rate cannot be calculated from the available data (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 Rybrila 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/ Adverse reaction	**Frequency**
Immune system disorder	
Allergic reaction	Uncommon

Nervous system disorder	
Headache	Unknown

Somnolence	Unknown
Drowsiness	Unknown
Seizure (worsening)	Uncommon
Dizziness	Unknown
Insomnia	Uncommon
Gastrointestinal disorder	
Dry mouth	Very common
Constipation	Very common
Diarrhoea	Very common
Vomiting	Very common
Pseudo-obstruction	Uncommon
Gastrointestinal mobility disorder	Uncommon
Eosophageal candidiasis	Uncommon
Breath odour	Uncommon
Nausea	Unknown
Infections and infestations	
Upper respiratory infection	Unknown
Pneumonia	Common
Otitis media	Unknown
Streptoccocal pharyngitis	Unknown
Urinary tract infection	Unknown
Psychiatric disorder	
Behavioural changes[2]	Very common
Eye disorder	
Nystagmus	Uncommon
Mydriasis	Unknown
Blurred vision	Unknown
Angle-closure glaucoma	Unknown
Photophobia	Unknown
Dry Eyes	Unknown
Cardiac disorder	
Flushing	Very common
Angioedema	Unknown
Transient bradycardia	Unknown
Respiratory, thoracic and mediastinal disorders	
Nasal congestion	Very common
Reduced bronchial secretions	Very common
Epistaxis	Unknown
Sinusitis	Unknown
Skin and subcutaneous tissue disorder	
Rash	Unknown
Hives	Uncommon
Skin dryness	Unknown
Sweat inhibition	Unknown
Renal and urinary disorders	
Urinary retention	Common
Urinary urgency	Uncommon
General disorders and administration site conditions	
Pyrexia	Common
Dehydration	Uncommon
Thirst	Uncommon

[1] Frequency categories are assigned from the pooled data from 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 glycopyrromium.

[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.
Any suspected adverse events should be reported to the Ministry of Health according to the national regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Since Rybrila 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

Rybrila is a synthetic muscarinic anticholinergic agent that binds competitively to the muscarinic acetylcholine receptor. Like other anticholinergic (antimuscarinic) agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the

atrioventricular node, exocrine glands and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions.

Aside from differences in the CNS actions, the spectrum of pharmacological actions by Rybrila is qualitatively similar to that of the naturally occurring alkaloids atropine and scopolamine, but differs with regard to duration and intensity. Within the peripheral nervous system, Rybrila acts as a potent competitive antagonist at muscarinic receptors and attenuates physiological processes regulated by the parasympathetic nervous system, including predictable actions within the respiratory tract, gastrointestinal system, and heart. The highly polar quaternary ammonium group of Rybrila limits its passage across lipid membranes, such as the blood-brain barrier.

Pharmacodynamic effects

In common with other anticholinergics, Rybrila has gastrointestinal, genitourinary, cardiovascular, respiratory, and ophthalmic effects. Due to its limited passage across lipid membranes, CNS effects such as drowsiness are unlikely. Specific known effects of Rybrila include dryness of the mouth, reduced bronchial secretions, dilation of pupils with loss of accommodation, photophobia, flushing, inhibition of sweating, transient bradycardia followed by tachycardia with palpitations and arrhythmias, urinary urgency and retention, reduced gastrointestinal motility and tone.

Clinical efficacy and safety

The medicinal use of Rybrila for its anticholinergic effects is well- established. Studies published in the scientific literature demonstrate reduction in gastric secretions and acidity, and delayed gastric emptying by Rybrila in peptic ulcer patients. Some efficacy of Rybrila as monotherapy was shown in peptic ulcer healing, recurrence rate of duodenal ulcer, chronic gastric ulcer, duodenal ulcer, peptic ulcer, gastrointestinal disorders and acid-peptic disease. Published studies of Rybrila in adults as add-on therapy with antacids in the treatment of peptic ulcer also demonstrate some efficacy.

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 Rybrila 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 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 ($p \leq 0.014$). 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).

The incidence of expected adverse events is dose-related. Therefore, dose is to be titrated to achieve an optimal balance of effectiveness with minimal anticholinergic associated adverse events.

There is no safety data available beyond 24 weeks treatment duration, therefore the treatment duration should be kept as short as possible.

5.2 Pharmacokinetic properties

Absorption

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

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.

Rybrila 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.

Distribution

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 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 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 Rybrila 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 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/1.73m2) and up to 2.2 fold in subjects with severe renal impairment or end stage renal disease (estimated GFR <30 mL/min/1.73m2). 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.

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

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

Biotransformation

In adult patients who underwent surgery for cholelithiasis and were given a single IV dose of tritiated glycopyrronium bromide, 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. Rybrila is excreted as one or more metabolites.

Elimination

A study using intravenous ^{3}H-glycopyrronium bromide 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 bromide. Following oral administration to mice, 7.6% was excreted in the urine and about 79% in the faeces.

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

5.3 Preclinical safety data

Non-clinical data, including genotoxicity or carcinogenicity studies have not been performed for Rybrila Oral solution.

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

Sorbitol Liquid (non-crystallising)
Glycerol
Citric acid monohydrate
Sodium Citrate
Sodium methyl parahydroxybenzoate (E219)
Sodium propyl parahydroxybenzoate (E217)

Strawberry flavour:
Flavouring substance
Maltodextrin (maize)
Acacia (E414)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

Once opened, the product may be stored for up to 28 days at a maximum of 25°C.

6.4 Special precautions for storage

Store below 25°C.
Do not freeze.
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

Rybrila oral solution is supplied in a 150 ml amber type III glass bottle with a tamper evident, child resistant cap.

Each bottle is provided in a cardboard carton along with a 15 ml syringe with graduations and a syringe adaptor to allow the correct dose to be measured.

6.6 Special precautions for disposal

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 the Rybrila Oral Solution 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

CTS Ltd.
4 Haharash St.
Hod-Hasharon
Israel

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