PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

Rybrila

Solution for oral administration

The active ingredient and its quantity:
Each 1 ml of solution contains 0.16 mg glycopyrronium (as bromide)
For a list of inactive ingredients and allergens in the preparation – see section 6.
Read the entire leaflet carefully before using the medicine.
This leaflet contains concise information about the medicine.
If you have any other questions, refer to the doctor or the pharmacist. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. What is the medicine intended for?

The medicine is intended for treatment of severe sialorrhea (excessive production of saliva) in children and adolescents aged 3 years and older with chronic neurological disorders.
Rybrila contains the active ingredient glycopyrronium bromide.
Excessive production of saliva is a common symptom of several diseases of the muscles or nerves. It is mainly caused by impaired control of the facial muscle system. Acute excessive drooling may be associated with inflammation or dental or oral infections. The active ingredient in Rybrila, glycopyrronium bromide, acts on the salivary glands to reduce the production of saliva.
Therapeutic class: anticholinergics or antimuscarinics

2. Before using the medicine

Do not use this medicine if:

- Your child has a sensitivity (allergy) to glycopyrronium bromide or to any of the other ingredients the medicine contains
- Your child has glaucoma (increased intraocular pressure)
- Your child has myasthenia gravis – a condition which leads to muscle weakness and fatigue
- Your child has an obstruction of the stomach or bowel causing vomiting, abdominal pain and paralytic ileus
- Your child has an enlarged prostate
- Your child has an inability to completely empty the bladder (urinary retention)
- Your child has a chronic end stage kidney disease that requires dialysis
- Your child is pregnant or breastfeeding
- Your child is taking potassium chloride solid dose preparations
- Your child is taking anticholinergic medicines

Special warnings regarding the use of the medicine
Before treatment with the medicine, tell the doctor if your child:
- Suffers from gastric reflux (a condition in which the stomach content backs up into the esophagus).
- Suffers from ulcerative colitis (a chronic inflammation of the colon which can cause abdominal pain, diarrhea and rectal bleeding).
- Has had a heart attack or suffers from a heart disease, irregular heart rate or high blood pressure, as the medicine can cause a change to the normal heart rate.
- Suffers from a faster heart rate than usual (a condition that can be caused by an overactive thyroid gland, heart failure or heart surgery).
- Is due to have surgery (including dental surgery) in which inhalation anesthetics will be used, as this medicine can cause a change to the normal heart rate.
- Suffers from diarrhea, especially if there is a stoma.
- Suffers from fever or if the external environmental temperature is high, as the medicine reduces sweating, thus impairing the body's ability to cool down.
- Suffers from a kidney disease, as the dosage of the medicine may need to be decreased.
- Suffers from damage to the blood-brain barrier.
- Suffers from intolerance to certain sugars, as this medicine contains sorbitol.

In addition, stop treatment and refer to the doctor if your child suffers from the following conditions:
- Seems unwell with a very fast or very slow heart rate.
- Constipation.
- Pneumonia.
- Behavioral changes.

After evaluating the events, the doctor will decide whether to continue treatment and whether there is a need to reduce the dosage.
If you are not sure whether any of the above conditions applies to your child, refer to the doctor or pharmacist before giving Rybrila.
Rybrila reduces the production of saliva which may increase the risk of dental disease; therefore, be sure to brush the teeth daily and have regular dental checks.
The efficacy and safety of Rybrila in long term use have not been studied beyond the recommended 24 weeks of treatment.
When used for a prolonged period, consult the pediatrician every 3 months.
Prolonged use should be done after consulting the pediatrician to check whether the medicine is still the appropriate treatment for your child.
Children and adolescents
Rybrila is not intended for children under the age of 3 years.
Drug interactions
If the child is taking or has recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.
Especially if he is taking:
- Other similar medicines such as oxybutynin: if the doctor instructs you to combine Rybrila with an additional similar medicine such as oxybutynin, it will be necessary to reduce the dosage due to an increased risk of side effects such as dry mouth, urinary retention and constipation when these similar medicines are administered together
- Antidepressants such as amitriptyline, clomipramine, lofepramine or imipramine (tricyclic antidepressants) or MAO inhibitors such as phenelzine, moclobemide, rasagiline, selegiline or tranylcypromine
- Phenothiazines such as chlorpromazine, fluphenazine, prochlorperazine or trifluoperazine which are used for treatment of mental problems or of nausea, vomiting or vertigo
- Antihistamines such as promethazine for treatment of allergies
- Parasympathomimetics such as carbachol, neostigmine or physostigmine which affect the transmission of nerve impulses to muscles
- Corticosteroids such as prednisolone for treatment of various conditions, including asthma and inflammation
- Inhalation anesthetics given before surgery (including at the dentist)
- Clozapine or haloperidol for treatment of schizophrenia
- Nefopam for treatment of acute and chronic pain
- Domperidone or metoclopramide for treatment of nausea and vomiting
- Amantadine or levodopa for treatment of Parkinson's disease
- Memantine for treatment of Alzheimer's disease
- Slow-dissolving digoxin tablets, disopyramide or atenolol, for treatment of heart problems
- Metformin for treatment of type 2 diabetes
- Glyceryl trinitrate tablets for treatment of angina pectoris. These may not dissolve properly under the tongue due to mouth dryness caused by the medicine
- Topiramate or zonisamide, for treatment of epilepsy and prevention of migraines
- Potassium chloride, including tablets [see section 2 "Do not use this medicine if"]
- Anticholinergic medicines

Use of the medicine and food
The medicine should be taken at least one hour before or two hours after a meal.
Avoid high-fat food. The presence of high-fat food reduces the bioavailability of the medicine if given shortly after a meal. Therefore, the medicine should be given at least one hour before or two hours after a meal. If the specific needs of the child require administering medicines with food, the medicine should be administered regularly at mealtime.
Pregnancy, breastfeeding and fertility
Rybrila should not be taken if your child is pregnant or breastfeeding.
Discuss the need to use contraception with the doctor.
Driving and operating machinery
Rybrila may make the patient feel drowsy, which can impair the ability to drive and operate machinery. Avoid activities that require alertness, such as driving and operating machinery, as long as these effects do not go away. Children should be cautioned against riding a bicycle or playing near a road etc.
Important information about some of the ingredients of the medicine
Rybrila contains sorbitol (E420). If you have been told by the doctor that your child has an intolerance to certain sugars, consult the doctor before taking the preparation.
Rybrila contains sodium propyl parahydroxybenzoate (E217) and sodium methyl parahydroxybenzoate (E219). These substances may cause an allergic reaction (even some time after taking them), and in exceptional cases bronchospasm (narrowing of the airways).
The medicine contains less than 23 mg of sodium per 1 ml, and is therefore considered sodium-free.

3. How should you use the medicine?

Always use the preparation according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the preparation.
The dosage and treatment regimen will be determined by the doctor only.
The medicine is for oral use only.
Instructions for use:
- Give the dose prescribed by the doctor 3 times a day.
- Remove the child-resistant cap from the bottle (A).

- Insert the syringe adapter with the hole into the bottle's neck (the pharmacist may have done that) (B).

- Insert the tip of the syringe into the opening in the bottle's neck, and make sure it is in place (C).

- To fill the syringe, turn the bottle upside-down. With the syringe held in place, gently pull the plunger downwards to draw the medicine up to the appropriate volume mark on the syringe. Check that the appropriate volume has been drawn (D). The maximum appropriate volume of the highest dose is 15 ml.

- Turn the bottle back upright and gently remove the syringe from the bottle's opening using a circular motion (E).

- Empty the contents of the syringe slowly and gently into the child's mouth.
- Leave the syringe adapter on the bottle's neck after use.
- Rinse the syringe thoroughly with warm water and dry it after every use.

If the child receives the medicine through a feeding tube, flush the tube with 20 ml of water after administering the medicine. The medicine is not intended for children under the age of 3 years.
Use in children and adolescents above the age of 3:
The initial dosage will be calculated based on the weight of the child.
The dosage will be determined by the doctor based on the table below and on the effect of the medicine and the side effects the patient is experiencing. The prescribed dose should be given 3 times a day (e.g., for a dosage of 1.5 ml, give 1.5 ml 3 X times a day).

Weight (kg)	Dose level 1 (ml)	Dose level 2 (ml)	Dose level 3 (ml)	Dose level 4 (ml)	Dose level 5 (ml)
13-17	1.5	3	4.5	6	7.5
18-22	2	4	6	8	10
23-27	2.5	5	7.5	10	12.5
28-32	3	6	9	12	15
33-37	3.5	7	10.5	14	15
38-42	4	8	12	15	15
43-47	4.5	9	13.5	15	15
≥48	5	10	15	15	15

Do not exceed the recommended dose.
If the child has taken an overdose or if a child has accidentally swallowed the medicine, refer immediately to a doctor or a hospital emergency room and bring the package of the medicine with you. An overdose increases the risk of experiencing side effects.
If you forget to give the medicine at the required time, give a dose as soon as possible. Afterwards, give the next dose at the usual time. However, if you forget to give the medicine and it is time to take the next dose, do not give a double dose; just give one dose.
Follow the treatment as recommended by the doctor.
Do not give medicines in the dark! Check the label and the dose <u>every time</u> you give a medicine. Wear glasses if you need them. If you have any other questions regarding the use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using Rybrila may cause side effects in some users. Do not be alarmed when reading the list of side effects, the child may not experience any of them.
If you notice any of the following serious side effects, **stop using the medicine and tell the doctor immediately:**
- Severe allergic reaction (swelling of the tongue, lips, face or throat) – unknown frequency
- Constipation – very common
- Urinary retention (inability to completely empty the bladder) – common
- Pneumonia – common
- Allergic reaction (hives, difficulty breathing or swallowing, itch) – uncommon
- Fever – common
- Behavioral changes such as mood change, irritability – very common

Additional side effects according to their frequency
<u>Very common side effects – effects that occur in more than 1 user out of 10:</u>
- Dry mouth
- Constipation
- Diarrhea
- Vomiting
- Behavioral change (behavioral changes include: nervousness, drowsiness, restlessness, hyperactivity, short attention span, frustration, irritability, mood swings, tantrums, unruly behavior, hypersensitivity, over-seriousness, sadness, frequent crying, cowardice)
- Flushing (redness)
- Nasal congestion
- Reduced secretions in the lower respiratory system

<u>Common side effects – effects that occur in 1-10 users out of 100:</u>
- Pneumonia
- Urinary retention
- High fever (pyrexia)

<u>Uncommon side effects – effects that occur in 1-10 users out of 1,000:</u>
- An allergic reaction
- Convulsion (worsening)
- Insomnia
- Pseudo obstruction of the gastrointestinal system
- Gastrointestinal motility disorder
- Esophageal candidiasis
- Bad breath
- Nystagmus (involuntary eye movements)
- Hives
- Urinary urgency
- Dehydration
- Thirst

<u>Side effects with unknown frequency (effects whose frequency has not yet been determined):</u>
- Headache
- Drowsiness
- Tiredness
- Dizziness
- Nausea
- Upper respiratory tract infection
- Middle ear infection (otitis media)
- Streptococcal throat infection
- Urinary tract infection
- Dilated pupils (mydriasis)
- Blurry vision
- Narrow-angle glaucoma
- Sensitivity to light
- Dryness in the eyes
- Angioedema
- Bradycardia
- Nose bleeding
- Sinusitis
- Rash
- Dry skin
- Sweat inhibition

If a side effect occurs, if one of the side effects worsens, or if your child suffers from a side effect not mentioned in this leaflet, consult your doctor.
<u>Reporting side effects</u>
Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or via the following link: https://sideeffects.health.gov.il/

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Do not use this medicine after the expiry date (exp.) appearing on the carton package and the bottle.
- Store in the original bottle at a temperature below 25°C.
- Do not freeze.
- Keep the medicine in the original package to protect from light.
- The medicine may be used up to 28 days after opening it for the first time.

6. Additional information

In addition to the active ingredient, the medicine also contains:
Sorbitol Liquid (non-crystallising), Glycerol, Citric acid monohydrate, Sodium Citrate, Sodium methyl parahydroxybenzoate (E219), Sodium propyl parahydroxybenzoate (E217), Flavouring substance Maltodextrin (maize) Acacia (E414) Triacetin (E1518)
What does the medicine look like and what are the contents of the package? the package contains a 150 ml amber-colored glass bottle containing a clear, colorless, strawberry flavored solution and a 15 ml syringe.
Marketing authorization holder and address: CTS Ltd., 4 Haharash St., Hod Hasharon, Israel
Name and address of the manufacturer:
Colonis Pharma Limited, 25 Bedford Square, Bloomsbury, WC1B 3HH, United Kingdom
Registration number of the medicine in the national drug registry of the Ministry of Health: 176-09-37799-99
This leaflet was checked and approved by the Ministry of Health in 04/2024.