COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rybrila 160 micrograms/ml oral solution (glycopyrronium bromide)

NL/H/5046/001/DC

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This module reflects the scientific discussion for the approval of Rybrila 160 micrograms/ml oral solution. The procedure was finalised on 27 May 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
Cmax	Maximum plasma concentration
CNS	Central Nervous System
CPRD	Clinical Practice Research Datalink
DUS	Drug utilisation study
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IP	Intraperitoneal
IV	Intravenous
LD^{50}	Median lethal dose
MAH	Marketing Authorisation Holder
PD	Pharmacodynamics
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PO	Per os
RH	Relative Humidity
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
Vd	Mean volume of distribution
Vss	Volume of distribution at steady state

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rybrila 160 micrograms/ml oral solution, from Clinigen Healthcare B.V.

The product 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.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of glycopyrronium bromide. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature. The MAH also submitted data showing that the bioavailability of Rybrila is similar to the bioavailability of the product most commonly studied in the scientific literature.

The concerned member states (CMS) involved in this procedure were Austria, Germany, Finland, France, Ireland, Norway and Sweden.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Rybrila is a clear, colourless, strawberry flavoured liquid. The oral solution has a pH between 3.5 and 4.5. It contains as active substance 200 micrograms of glycopyrronium bromide equivalent to 160 micrograms of glycopyrronium.

The pharmaceutical form is packed in a 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.

The excipients are: glycerol, sorbitol (E420), sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), citric acid monohydrate (E330), trisodium

citrate dihydrate (E331) and strawberry flavour (flavouring substance, maltodextrin (maize), acacia (E414), triacetin (E1518)).

II.2 Drug Substance

The active substance is glycopyrronium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder and is freely soluble in water. Glycopyrronium bromide contains two asymmetric carbons; the product is a 50/50 % mixture of enantiomers, thus the product is not optically active. As the product is a solution, particle size and polymorphism are not of concern.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur and additional requirements for microbial contamination. Batch analytical data demonstrating compliance with the specifications have been provided for three batches.

Stability of drug substance
The active substance is stable for five years when stored in double polyethylene bags placed in a cardboard drum. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP. A storage condition of not more than 25°C with excursions up to 40°C is proposed. The drug substance should be protected from light.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. Preservative solubility in the individual solvents of the proposed formulation was examined. Palatability and taste masking capacity of the

prototype formulations was checked by a test panel and stability studies were performed at different temperatures. The most suitable pH was examined for the formulation. In addition, a scale up of the prototype formulation was performed, without affecting any of the tested parameters. No overages are used in the manufacture of the drug product formulation.

Manufacturing process

The manufacturing process consists of dispensing and dissolving of the raw materials, adjustment of pH, filtration of the bulk solution and filling of the bottles. The product is manufactured using conventional manufacturing techniques. Process validation on three full-scale batches has been performed.

Control of excipients

All the excipients (except the strawberry flavour) comply with Ph.Eur. requirements. The strawberry flavour complies with the requirements of European regulations on food additives. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity tests by high-performance liquid chromatography (HPLC) and ultraviolet (UV) light for drug substance and preservatives, assay also for drug substance and preservatives, related substances, pH, microbial limits, uniformity of mass of delivered dose and fill volume. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scale batches stored at 25°C/60 % RH (up to 24 months), 30°C/65 % RH (up to 12 months) and 40°C/75 % RH (up to six months). The conditions used in the stability studies are according to the ICH stability guideline, and the product specifications remained between the set limits. Although the photostability study was not performed in accordance with ICH recommendations, this was considered sufficient. On basis of the data submitted, a shelf life was granted of 24 months. The storage conditions are: “Store below 25°C. Do not freeze. Store in the original bottle. Keep bottle in the original carton in order to protect from light.”
Following first opening of the multidose container, an in-use shelf life of 28 days has been granted when stored at a maximum of 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rybrila has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This well-established use application contains detailed references to published literature on non-clinical aspects, as well as other evidence obtained from expert committee reports and published product monographs of licensed products. The information presented for the non-clinical pharmacology section was based on relevant scientific literature over the period of 1960 up to very recent. The MAH has performed a study to determine potential ecotoxicity of the active substance.

III.2 Pharmacology

III.2.1 Pharmacodynamics

III.2.1.1 Primary pharmacodynamics

The mode of action, similar to atropine, is on the peripheral cholinergic receptors that 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 (Barocelli et al., 1993, Franko et al., 1960 in Rumpler et al., 2014). Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions Glycopyrronium Bromide antagonizes muscarinic symptoms (e.g. bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases (Centre for Drug Evaluation and Research, 2012 in Garnock-Jones, 2012).

In vitro studies

In *in vitro* studies under physiological conditions using Chinese hamster ovarian cells glycopyrronium bromide binds with high affinity to the muscarinic acetylcholine receptors M1, M2 and M3, and has 4- to 5-fold higher selectivity for human M1 and M3 receptors than for the human M2 receptor (equilibrium binding affinity constants of 9.60-9.81 and 9.47-9.64 vs. 8.70-9.25) (Carter, 2013; Sykes et al., 2012). In addition, glycopyrronium bromide dissociates slower from the M3 and M1 receptors than from the M2 receptor (dissociation half-life 11.4 and 13.9 vs. 1.07 min; kinetic off rate 0.061 and 0.05 vs. 0.646 per min (Sykes et al., 2012 in Carter, 2013). *In vitro* studies with rat tissues showed that there are different binding affinities depending on the location of the muscarinic receptors (Ogoda et al., 2011).

In vivo

The gastric anti-secretory activity of glycopyrronium bromide was shown in the pyloric-ligated rat, where an oral dose as low as 5 mg/kg was sufficient for significantly lowering both volume and free acidity of gastric secretion (Franko et al., 1962). Intragastric glycopyrronium bromide, 1 mg/kg as the base, was very effective in reducing volume and acidity of basal secretion in rats. The effect of atropine, glycopyrronium bromide, metoclopramide and cisapride on the antral motility was investigated in eight dogs (four Beagles and four Labradors) using passive telemetry. Both anticholinergics induced a pronounced and lasting reduction of the intensity and frequency of the contractions. A definite dose-related inhibition of the antral motility was seen in Beagles, similar for both active substances (Burger et al., 2006). The charcoal meal progression test in rats indicated that glycopyrronium bromide affected gastrointestinal propulsive activity. Inhibition of intestinal motor activity was likewise shown in Thiry-Vella fistula dogs (Franko et al., 1962). The effects of atropine and glycopyrronium bromide on oesophageal, gastric, and tracheal pH, heart and respiratory rates, and the incidence of silent oesophageal reflux under anaesthesia were determined in forty mature, young, adult dogs (15 males, 25 females) scheduled to undergo anaesthesia and surgery (Roush et al., 1990).

III.2.1.2 Secondary pharmacodynamics

Sialorrhea

The antisialagogue actions of these antimuscarinic drugs have been studied in animals more as a surrogate of potential adverse effects of inhaled drugs in the treatment of COPD. The results of this representative anti-sialagogue experiment show that glycopyrronium bromide, when administered intravenously in dogs at a dose of 5 µg/kg, was capable of diminishing the volume of salivary secretion by approximately two thirds after 40 minutes, which was stimulated by methacholine (11µg /kg) (Franko et al., 1962). The lung and submaxillary gland (SMG) concentrations of glycopyrronium correlated (r2 = 0.6 and 0.5, respectively) with its broncho-protective and antisialagogue effects respectively. Experiments showed that glycopyrronium bromide was an effective antagonist of those symptoms that are presumably peripherally mediated, including salivation (Pulido-Rios et al., 2013).

Respiratory effects

Glycopyrronium bromide concentration-dependently inhibited electrical field stimulation-induced (Haddad et al., 1999) and carbachol-induced (Villetti et al., 2006) contraction of human isolated airways at nanomolar concentrations. Glycopyrronium bromide inhibited the broncho constrictive effect of methacholine in a dose-dependent manner in rats (Pulido-Rios et al., 2013).

Anaesthesia

Glycopyrronium bromide was found to possess local anaesthetic properties in both tests that were used for this activity in guinea pigs and rat (Franko et al., 1962).

Other effects

Glycopyrronium bromide in low concentrations antagonised the spasmogenic effect of acetylcholine in isolated pig ileum (Franko et al., 1962). Glycopyrronium bromide appeared to be an inhibitor of parasympathetically mediated effects in mice. Methacholine-induced lacrimal hypersecretion was antagonized by glycopyrronium bromide in rat (Franko et al., 1962). Glycopyrronium bromide seemed to influence heart and respiration rates, and frequency of bowel movements were performed in six Thoroughbred horses (Rumpler et al., 2014). In anaesthetised dogs, intravenous doses (5 to 10 µg/kg) or oral doses (0.5 to 5 mg/kg) of glycopyrronium bromide markedly reduced intestinal tone and moderately inhibited amplitude of intestinal contractions, but they had essentially no effect on respiration, carotid arterial blood pressure, or cardiac rate (Franko et al., 1962).

III.2.1.3 Safety pharmacology

Safety pharmacology in animals for glycopyrronium bromide was retrieved from literature published over the period from 1960 to 2018, which was accepted. Furthermore, there is wide clinical experience with glycopyrronium bromide, which will complete and supersede (the need for) non-clinical safety data as presented in the following paragraphs.

Mydriasis, xerostomia, and lack of pupillary accommodation to light, for example, were rarely observed when a dose of 1 mg/kg of glycopyrronium bromide was given via the oral route to chronic pouch dogs (Franko et al., 1962).
Upon to administrating adult Thoroughbred horses by constant-rate intravenous infusion (4 µg/kg/h glycopyrronium bromide for 2 h, obvious hysteresis was observed when heart rate and plasma glycopyrronium bromide concentrations were plotted against time and when the effect was plotted against plasma glycopyrronium bromide concentrations that were minimized by the incorporation of an effect compartment model. The hysteresis has been successfully modelled by the effect compartment approach, which postulates the existence of a hypothetical effect compartment linked to the plasma site by a first-order process (Rumpler et al., 2014).

It has been well known that glycopyrronium bromide and other competitive muscarinic receptor antagonists prevent the action of acetylcholine on the SA node of the heart [Adams (Ed.) (2001) in Rumpler et al (2014)]. As a result, physiological responses to parasympathetic (vagal) nerve impulses are thereby attenuated or abolished. Furthermore, as muscarinic receptors are also present in the peripheral vasculature, the effects of glycopyrronium bromide on heart rate may account for partial subsequent and measurable effects of the drug on the cardiovascular system.

The poor penetration of glycopyrronium bromide into the CNS was further demonstrated in un-anaesthetised, curarized cats (Franko et al., 1962).

III.2.2 Pharmacokinetics

Glycopyrronium bromide is absorbed in pharmacologically effective amounts from the gastrointestinal tract. The absorption of glycopyrronium bromide depends on administration route, as does the distribution. Very limited data is available on absorption, distribution, metabolism and excretion of orally administered glycopyrronium bromide in animals with the majority of studies being performed either parenterally or by inhalation/nebulisation. The information for the non-clinical pharmacokinetic section was based on relevant scientific literature over the period of 1960 up to very recent, which could be endorsed.

III.2.2.1 Absorption

Absorption, distribution and metabolism have been studied with intravenous administered 14C-labelled glycopyrronium bromide in mice (Kagiwada et al., 1973 in Mirakhur et al., 1983). Following intravenous administration, peak radioactivity was found in all organs at 5-10 minutes except brain: liver, kidney and intestines showed traces of activity at 24 hours. Following oral administration, measurements in the stomach and small intestine showed that the maximum amount of radioactivity and absorption from the gastrointestinal tract were poor (Kagiwada et al., 1973 in Mirakhur et al., 1983).

III.2.2.2 Distribution

Glycopyrronium bromide disposition in the horse following a constant-rate intravenous infusion (CRI) distributed rapidly from the central to the peripheral compartments as demonstrated by the initial disposition phase median half-life of 0.12 h (Rumpler et al., 2011). The fraction of glycopyrronium bromide bound to plasma protein over a range of plasma drug concentrations (0.1-25 ng/mL) was 37-44%. In dogs, average CSF levels of glycopyrronium bromide over a four-hour period did not exceed 0.9 ng/ml, with a CSF/serum peak ratio of 0.1 for glycopyrronium bromide seen at a four-hour post-drug interval (Proakis et al., 1978). Although the glycopyrronium bromide fetal serum/maternal serum concentration ratios increased with time, the highest fetal serum level (0.63 ± 0.07 ng/ml) occurred four hours after drug administration and represented less than 5 per cent of the corresponding maternal serum concentration in dogs (Proakis et al., 1978).

III.2.2.3 Metabolism

Studies of the metabolism of glycopyrronium bromide in animals indicate the major metabolic pathway to be the nonenzymatically hydroxylation of the cyclopentyl ring and the oxidation of the hydroxyl group in the mandelic acid residue (Takada et al., 1973 in Mirakhur et al., 1983). This leads to the formation of the major circulating metabolite M9, which is a racemic carboxylic acid derivative (Santus et al., 2017), and has been mainly detected in the liver and kidney (Mirakhur et al., 1982 in Mirakhur et al., 1983). M9 has a plasma concentration that is approximately the same as that of the parent drug after inhalation but not after intravenous administration, but this metabolite was shown to be inactive against all tested targets *in vitro* (Carter, 2013). Glycopyrronium bromide also forms various mono and bis-hydroxylated metabolites *in vitro*. Several cytochrome p450 (CYP) enzymes are thought to contribute to the oxidative biotransformation of glycopyrronium bromide with the most quantitatively important cytochrome being CYP2D6 (Santus et al., 2017).

III.2.2.4 Elimination

Following oral administration to mice, 7.6 % was excreted in urine and about 79 % in faeces (Kagiwada et al., 1973 in Mirakhur et al., 1983). Systemically available glycopyrronium is predominantly (60-70 %) cleared from the plasma via renal elimination of the parent drug (Carter, 2013). Other elimination routes are mainly metabolism and biliary excretion (Kaltiala et al., 1974 in Mirakhur et al., 1983).

III.2.2.5 Pharmacokinetic interaction studies

Non clinical data on PK drug interaction studies was not provided, which can be agreed as it is rather considered an aspect to be addressed in the clinical part of the dossier.

III.3 Toxicology

The information for the non-clinical toxicology section was based on scientific literature over the period of 1960 up to very recent. It is regarded a well-established medicine as defined by the appropriate legislation from its initial approval in the 1960s. Since then, also safety data in human has been collected. This approach and the reflection of the safety of glycopyrronium bromide in animals and translation to humans is considered appropriate.

III.3.1 Acute or single dose toxicity studies

Data on the acute toxicity of glycopyrronium bromide was retrieved from literature publications on studies dating from 1962-1973 (before Good Laboratory Practice got introduced). This was agreed. However, it has to be noted that information on the median lethal dose (LD^{50}) is nowadays no longer required.

The MAH made reference to The Registry of Toxic Effects of Chemical Substances database of the National Institute of Occupational Safety and Health (NIOSH) in the USA, which has listed single dose-toxicity data from studies conducted with glycopyrronium bromide (RTECS, 2014). In the overview, for each study information is given on the test subject species, dosage, route of administration and reported effects.

Also, reference was made to Franko et al. (1962), who have conducted acute and single dose toxicity studies by the PO (per os/oral), IV (intravenous), IP (intraperitoneal) and SC (subcutaneous) routes in mice and rats, PO and IV in rabbits, and IV in dogs and cats. Animals of both sexes were used except for the IV rat and PO rabbit experiments (males only); there were no notable sex differences. Administration by the IV route was most toxic, with reported LD^{50} values of 14-16 mg/kg for mice and rats, approximately 25 mg/kg for rabbits and approximately 15-30 mg/kg for dogs and cats (Franko et al., 1962). When glycopyrronium bromide was administered orally, the LD^{50} increased to 900-980 mg/kg in mouse, 1600-1800 mg/kg in rat and to 2400 mg/kg in rabbit. These doses are 80-750 times greater than the maximum recommended human dose on a mg/kg bodyweight basis. Median lethal doses by the per oral route were >30 times greater compared with clinical signs produced by treatment, including mydriasis, decreased motor activity, hyperreflexia, laboured respiration, tremors, and tonic and clonic convulsions in the species studied. These clinical signs are recognised as classic anticholinergic effects.

III.3.2 Repeat-dose toxicity studies

The MAH referred to five sub-chronic and chronic repeat-dose toxicity studies conducted by Franko et al. (1970) using Sprague Dawley rats and Beagle dogs. Overall, no toxicologically significant effects were observed in the repeat-dose (sub-chronic and chronic) toxicity dietary studies of Franko et al (1970). Mydriasis, cycloplegia, occasional lacrimation, injection of sclera, rhinorrhoea, occasional tachycardia, emesis and xerostomia were noted in Beagles dogs dosed intravenously. Results were essentially negative with respect to clinical laboratory investigations, body weight and food consumption findings, gross pathology, organ weights and histopathology. Only slight changes in body weight, food consumption and in a number of haematology parameters were observed in some studies.

Further, reference was made to a subacute and chronic repeat-dose toxicity study performed by Saito et al. (1973), using Wistar rats. In the sub-acute toxicity study, the rats were dosed with glycopyrronium bromide at 22, 46, 100 and 220 mg/kg/day for 30 days. Only mydriasis was seen in all dose groups. In males of the 220 mg/kg high dose group, a slight fall in erythrocytes, a relative fall in the albumin/globulin ratio and a slight but not toxicologically significant increase in transaminase activities was observed. Absolute increases in prostate weight (male), thymus weight (female) and adrenal and liver weight were noted. Histopathological, hyperaemic and haemostatic changes in a range of tissues including lymph node, epithelial cell proliferation in the medullary cord, dilation of the sinus, reticuloendothelial cell proliferation, and erythrophagocytosis migration, and in the spleen, proliferation of splenic white-pulp cells, and of splenic red-pulp medullary cord cells were noted mainly in high dosed males. Vacuole clouding in adrenocortical fasciculate zone cells, simple atrophy of gastric mucosal epithelial cells and catarrhal detachment of duodenal mucosa, swelling of the tubular epithelium, proteinaceous casts in the tubuli, and hepatic cell vacuole clouding were also noted (Saito et al., 1973).

In the chronic repeat-dose toxicity study performed by Saito et al. (1973), Wistar rats were administered 10, 22, 46 and 100 mg glycopyrronium bromide per kg/day for 180 days. Here, mydriasis was also found without any other adverse symptoms were observed. In males, a dose-dependent slight suppression of body weight was seen, with no adverse effects on food consumption. A slight increase in neutrophils in males and indications of slight anaemia in the female high dose (100 mg/kg/day) groups as well as relative increases in weight of livers (male), hearts and ovaries (female) and adrenals (female 100 mg/kg) were observed. Dose-dependent hyperaemia and haemostasis in all organs, and in high dose groups reticuloendothelial cell activation in the lymph node and spleen, vacuole clouding in the adrenal gland, simple atrophy of gastric mucosal epithelial cells, expansion or swelling of the tubular epithelium and proteinaceous casts in the tubuli were seen. Recovery from almost all of the above changes were found, and no other pathological changes were observed.

<u>Translation of animal toxicological data to the human population including paediatrics</u>

The clinical safety findings for glycopyrronium bromide are in accordance with its anticholinergic pharmacological effects, with no evidence of off-target toxicological effects observed. The toxicological findings of human studies in the target population, including

paediatrics, are discussed the clinical AR and shows a similar safety profile to that as seen in the animal studies.
The repeated dose toxicity of glycopyrronium bromide in animals and in peadiatric and adult humans as present in literature have been summarised to a sufficient extent and does not point to unexpected safety risk for the human population including peadiatrics.

III.3.3 Genotoxicity

It has been shown through the development of oral, topical and inhaled glycopyrronium bromide over the last 15 years that the molecule did not elicit any genotoxic effects in the Ames mutagenicity assay, the human lymphocyte chromosome aberration assay, or *in vivo* clastogenicity (rat bone marrow micronucleus assay) (Health Canada, 2017). Based on assays, the molecule would be classified as non-cytotoxic. The results from the *in silico* toxicological assessments performed (*In Silico* Toxicology Consultancy Report using Derek Nexus and Leadscope; ForthTox Report – July 2015) show no alerts for all genotoxicity, mutagenicity and carcinogenicity end-points evaluated as expected. It has been made sufficiently clear, using literature data, that glycopyrronium bromide is not mutagenic.

III.3.4 Carcinogenicity

Glycopyrronium bromide has not been listed as a potential carcinogen by the International Agency for Research on Cancer, the European Union, the American Conference of Governmental Industrial Hygienist, the National Toxicology Program or the Occupational Safety and Health Administration. Data has been reviewed from other public available resources, including other glycopyrronium bromide dosage forms from around the world, which do not indicate glycopyrronium bromide to be a carcinogen.

Carcinogenicity studies of glycopyrrolate did not result in an increase in the incidence of tumours in a 2-year inhalation study of glycopyrrolate in Wistar rats at doses up to 0.56 mg/kg/day, approximately 143 times the maximum recommended dose of a nebulized solution of glycopyrronium bromide in adults on an AUC basis. Also, no evidence of tumorigenicity occurred in a 26-week oral (gavage) study in male and female TgrasH2 mice that received glycopyrrolate at doses up to 93.8 and 125.1 mg/kg/day, respectively, approximately 66 times the maximum recommended daily dose of nebulized glycopyrronium bromide (FDA Lonhala Magnair, 2017). In a six-month study by the oral route in transgenic mice (rasH2) and a two-year inhalational study in rats no signs of carcinogenicity were observed either. The relative systemic exposure reached was ≤71 in male mice (75 mg/kg/day per os), ≤53 in female mice (100 mg/kg/day per os) and ≤79 in rats (≤0.45 mg/kg/day by inhalation) and the relative local exposure in the rat study was ≤194.
The use of the oral route for the transgenic mouse study is considered acceptable given that the model has not yet been validated for inhalation and that no respiratory tract neoplasia occurred in rats. Non-neoplastic lesions were observed in the stomach of mice (epithelial hyperplasia, hyperkeratosis and mixed cell infiltration) and are consistent with local irritation following oral administration at high doses (PFSB Japan, 2012). There is no evidence to suggest that glycopyrronium bromide when administered orally is a carcinogen. It has been made sufficiently clear based on literature data that (orally administered) glycopyrronium bromide is not carcinogenic.

III.3.5 Reproduction toxicity

Developmental toxicity

Developmental toxicity data for glycopyrronium bromide have been reported by Kagiwada et al. (1973) using Wistar rats and ICR-Jcl mice. Pregnant ICR-Jcl mice were orally dosed with glycopyrronium bromide from Day 7 to 12 of gestation at 4, 20 or 100 mg/kg/day, which appeared not to result in maternally toxic effects, reproductive effects, developmental/teratogenic foetal and offspring effects. Pregnant Wistar rats were orally dosed with glycopyrronium bromide from Day 9 to 14 of gestation at 4, 25 or 150 mg/kg/day, which appeared not to result in reproductive toxicant or developmental/teratogenic foetal or offspring effects. At this high dose, glycopyrronium bromide induced limited maternal toxicity at the initiation of dosing such as reductions in body weight and food consumption.

Effects on Reproductive Toxicity

A multi-generation reproductive toxicity study was performed in rats (20 sex/dose) using the dietary route of exposure (Franko et al., 1970). Dose levels of glycopyrronium bromide were 0 and 63 ppm for the first litter, 0 and 130 ppm for the second generation, and 0 and 32.5 ppm for the third generation. No effects on fertility and reproductive performance occurred in male and female rats at a subcutaneous glycopyrrolate dose of 0.63 mg/kg/day, which is approximately 384 times the recommended maximum dose of nebulized glycopyrronium bromide on an AUC basis (FDA Lonhala Magnair, 2017).

Effects on Lactation

The effect of glycopyrronium bromide on lactation was examined in a study by Ishizaki et al. (1978). Glycopyrronium bromide was dosed orally 0, 1, 10 and 100 mg/kg, and on day 13 or day 14 after delivery the sucklings were separated from dams, followed by immediate oral administration of glycopyrrolate. Glycopyrronium bromide had no effect on the amount of milk, however, the body weight of dams in the 100 mg/kg group at 6 hours after administration was decreased. The weight of mammary glands in the 10 and 100 mg/kg groups were significantly lower than the mammary gland weight of the control group (Ishizaki et al., 1978).

Foetal risk summary

In pregnant sheep and dogs, the transfer of glycopyrronium bromide across the placenta was significantly less than that of atropine (Murad et al., 1981 in Briggs et al., 2011). No change in maternal or fetal arterial pressure, fetal heart rate, or beat-to-beat variability was observed in pregnant sheep .

In human, a possible association with glycopyrronium bromide use in the third trimester and minor malformations was found (Heinonen et al., 1977 in Briggs et al., 2011). Maternal heart rate, but not blood pressure, was increased. No effects on foetus or in the new-borns were observed (Diaz et al., 1980, Abboud et al., 1981, Roper and Salem., 1981, Abboud et al., 1983 in Briggs et al., 2011). Glycopyrronium bromide has been recommended as the

anticholinergic of choice during anaesthesia for electroconvulsive therapy in pregnant patients (Wise et al., 1984 in Briggs et al., 2011).

Breastfeeding
No reports have been found describing the use of glycopyrronium bromide during human lactation (Briggs et al., 2011).

Fertility
Diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Diminished seminal secretion was observed upon high doses of glycopyrronium bromide in dogs. Decreased birth weight and postnatal body weight gain were observed in the offspring of rats upon subcutaneous administration at 1.5 mg/kg/day during gestation and lactation (Health Canada, 2017).

Furthermore, as for the single dose toxicity study, the MAH referred to the RTECS (2014), which has listed reproductive and developmental toxicity data from studies conducted with glycopyrronium bromide.

III.3.6 Other studies

Combination studies
Combination studies with other drugs and glycopyrronium bromide did not suggest glycopyrronium bromide to significantly influence the lethality of the drugs with which it was combined.

Excipients and Impurities
Excipients Glycerol, Sorbitol 70 %, Sodium methyl parahydroxybenzoate, Sodium propyl parahydroxybenzoate, Strawberry flavour, Citric acid monohydrate and Trisodium citrate dehydrate are widely used and are, except Strawberry flavour, Ph.Eur. listed.

The strawberry flavour used in the manufacture of Glycopyrronium Bromide 1mg/5ml oral solution complies with the requirements of Regulation (EC) No 1334/2008 on flavourings, Regulation (EU) No 872/2012 and Regulation (EC) No 1333/2008 on food additives and prior to release tested, providing a certificate of analysis.

Several impurities in the active ingredient glycopyrronium bromide are tested and limited (according Ph. Eur. specifications) by the manufacturer using HPLC method.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH has performed a study to Good Laboratory Practices to determine the *n*-octanol/water partition coefficient(s) (log *K*ow) of glycopyrronium bromide.
The study results are summarised in Table 1.

Table 1. Summary table of ERA

Substance (INN/Invented Name): glycopyrronium bromide			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OECD107	Log D_{ow} =-1.6 to 0 for pH 5, 7 and 9	Potential PBT: No
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, refined	0.00135	µg/L	> 0.01 threshold: No

Conclusions on ERA:
Glycopyrronium bromide PEC surface water value is below the action limit of 0.01 µg/l and is not a PBT substance as log K_{ow} does not exceed 4.5.

III.5 Discussion on the non-clinical aspects

This application refers to a medicinal product where the active substance has a well-established medicinal use in the meaning of Commission Directive 2001/83/EC, with recognised efficacy and an acceptable level of safety. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided which is based on up-to-date and adequate scientific literature, with references from 1960 up to very recent. This overview justifies why there is no need to generate additional non-clinical data on pharmacology, pharmacokinetics and toxicology. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Glycopyrronium bromide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. A scientific 'bridge' to the published literature is provided in the form of a bioequivalence study comparing the drug product to the product most commonly studied in the published scientific literature. The bioequivalence study is discussed below. The scientific overview justifies why there is no need to generate additional clinical data, therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

IV.2.1 Scientific overview

IV.2.1.1 Absorption

Absorption of oral administered glycopyrronium bromide is adequately described. It demonstrates a low and variable bioavailability. A high-fat meal decreases bioavailability of glycopyrronium bromide, co-administration with food should be avoided (Garnock-Jones, 2012; Eiland, 2012).

IV.2.1.2 Distribution

Glycopyrronium bromide demonstrates rapid distribution. The MAH referred in the clinical overview to studies on children and adults (Garnock-Jones, 2012; Rumpler et al., 2014).

IV.2.1.3 Metabolism

Glycopyrronium bromide is hydrolysed to form the major circulating metabolite, M9 (Santus et al., 2017). Several cytochrome P450 (CYP) enzymes are thought to contribute to the oxidative biotransformation of glycopyrronium bromide (Carter, 2013). More data on metabolism is given in paragraph III.2.2.3.

IV.2.1.4 Elimination

Systemically available glycopyrronium bromide is predominantly cleared from the plasma via renal elimination of the parent compound (Kaltiala et al., 1974; Ali-Melkkila et al., 1990; Kirvela et al., 1993; Carter, 2013).

IV.2.1.5 Pharmacokinetics in special populations

Elimination of glycopyrronium bromide is likely to be impaired in patients with renal failure and therefore, it is proposed to contraindicate the use of glycopyrronium bromide in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2), urinary retention and uraemia. For patients with less severe renal impairment, it is stated that reduction of doses should be considered, which is acceptable. For patients with hepatic impairment the elimination of glycopyrronium bromide is not likely to be impaired, therefore, it was agreed that the following is included in the SmPC: 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.

Further, the MAH has submitted data that describe the impact of weight on the pharmacokinetics. The bioavailability of glycopyrronium bromide remains low in children as it does in adulthood; however, longer elimination half-lives and larger Vd have been seen in younger children suggesting a higher systemic exposure in those who weigh less (Rautakorpi et al., 1994; Rautakorpi et al., 1998; Garnock-Jones, 2012; Eiland, 2012). The variability seen in bioavailability combined with the non-linear pharmacokinetics (PK) profile necessitates a titration dosing schedule starting at the minimum dose determined by the patient's weight. Although there does appear to be some effect of weight on certain PK parameters such as Vd/Vss, weight does not appear to significantly affect PK parameters to any great degree.

The higher volume of distribution and lower clearance may result in a longer elimination half-life, however, it is not expected that this would have any impact on the dosing recommendations as dose is titrated to therapeutic effect against unwanted effects.

Pharmacokinetics in the elderly is not described as the product is only intended for children and adolescents aged 3 years and older, this is acceptable. The MAH has described the lack of published literature on glycopyrronium bromide pharmacokinetics during pregnancy and lactation. Glycopyrronium bromide crosses the placenta to a limited extent, but it is not known whether it is distributed into milk and no reports describing the use of glycopyrronium bromide during human lactation have been located (Briggs et al., 2011). Therefore, the SmPC contains a statement advising not to use the product during pregnancy or breast feeding, which has been accepted.

Consequences of possible genetic polymorphism, and pharmacokinetics of metabolites were not described, which is acceptable.

IV.2.1.6 Interactions

Several potential interactions have been described in published literature, and the relevant interactions are included in the SmPC. The SmPC contains adequate contraindications and warnings with regards to such interactions.

IV.3 Bridging data of the products in the application with the products referred to in the literature

As the current procedure relies on published scientific literature, a scientific 'bridge' to the published literature is provided in the form of a comparative bioavailability study, comparing the drug product to the product most commonly studied in the scientific literature. In this bioequivalence study, the pharmacokinetic profile of the test product Rybrila 160 micrograms/ml oral solution (Clinigen Healthcare B.V., The Netherlands) is compared with the pharmacokinetic profile of the US product Cuvposa oral solution 1 mg/5 ml (Merz North America, Inc., USA). The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, replicate design comparative bioequivalence study was carried out under fasting conditions in 68 healthy subjects, aged 18-59 years. Each subject received a dose of 10 ml containing 2 mg of the active substance, of one of the two formulations. The solution was orally administered with 200 ml water after a fasting period of at least ten hours. There were four dosing periods, separated by a washout period of at least five days. Blood samples were collected pre-dose and at 0.25, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 16 and 24 hours after administration of the product. The design of the study is acceptable. The fasting condition has been justified on the ground that high fat food reduces the oral bioavailability of glycopyrronium bromide if given shortly after a meal.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

From the 68 study objects, 66 subjects have completed the study and two subjects were withdrawn due to personal reasons and an adverse event. 67 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of glycopyrronium bromide under fasted conditions.

Treatment N=67	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	2642.82 ± 1636.93	2799.49 ± 1735.92	419.80 ± 268.87	0.75 (3.00 - 6.07)
Reference	2490.29 ± 1525.31	2671.43 ± 1628.85	410.96 ± 256.87	0.75 (3.50 - 6.02)
***Ratio (90 % CI)**	1.066 (1.004 – 1.132)	--	1.015 (0.951 – 1.082)	--
CV (%)	30.1	--	32.3	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90 % confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Rybrila is considered bioequivalent with Cuvposa.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.4 Clinical efficacy

The MAH provided bibliographic data to support the efficacy of glycopyrronium bromide for sialorrhoea. The proposed dosing regime and titration schedule is derived from Cuvposa. Since the bioequivalence study has shown that Rybrila and Cuvposa are bioequivalent, the dosing regime is considered supported.

Studies by Zeller et al. (2012b), Parr et al. (2017) and Mier et al. (2000) are considered as the main studies supporting the efficacy of glycopyrronium bromide for the treatment of sialorrhoea. These studies did have a randomized placebo or comparator controlled design. The results from the studies by Zeller et al. (2012b), Parr et al. (2017) and Mier et al. (2000) show that short-term treatment with glycopyrronium bromide improved excessive drooling in paediatric patients with neurological disorders.

In the Zeller study (2012b), glycopyrronium bromide (Cuvposa) was evaluated against placebo in a cohort of 38 patients. The study showed an effect of glycopyrronium as early as two weeks and the improvement on drooling was sustained until the end of the study at 8 weeks. Most of the investigators and caregivers/parents also deemed the glycopyrronium treatment as “worthwhile” (~85-100 %) (Zeller et al., 2012b).

In the Parr study (2017), glycopyrronium bromide liquid was evaluated against a hyoscine skin patch, which is another anticholinergic drug. The study design was a comparative effectiveness trial, therefore no placebo arm was included. Both treatment arms improved excessive drooling over the course of 12 weeks. There was no difference between the groups in terms of efficacy outcomes (no statistical significant difference). Note it is unclear whether the formulation of the glycopyrronium liquid is the same as Rybrila (Parr et al., 2017).

In the Mier study (2000), glycopyrronium capsules were evaluated against placebo in paediatric patients. Eight weeks of glycopyrronium treatment produced a statistical significant improvement of excessive drooling compared to placebo. The information regarding the included patient population is limited. Moreover, the study used capsules whereas Lycopax is an oral solution (Mier et al., 2000)

Furthermore, the MAH provided supportive studies, which all have either an open-label or a prospective/retrospective cohort design. In a few of the studies, the formulation is not specified or is different than the Rybrila formulation (e.g. Montgomery, 2016; Blasco and Stansbury, 1996; Stern, 1997; Reid, 2019). In addition, some of the older publications provide only limited methodological information (e.g. Stern, 1997; Blasco and Stansbury, 1996). Overall, no conclusions with regards to efficacy can be drawn from the supportive studies due the limitations of the trial designs.

IV.5 Clinical safety

The summary of clinical safety as provided by the MAH is based upon the following information:

- A systematic review of the literature containing safety data for glycopyrronium bromide used to treat sialorrhoea in children of three years of age and above.
- Safety data generated during a study using the Clinical Practice Research Datalink (CPRD) of the prescribing in primary care of glycopyrronium bromide oral solution or suspension to children between the age of 3 and 18 years of age from January 1987 to April 2018.
- Safety data generated during the previously discussed bioequivalence study.
- A review of the MHRA adverse drug reactions database for spontaneous reports associated with glycopyrronium bromide used systemically as a solution or suspension.
- A review of the cumulative post-marketing data in the company safety database.

For the clinical safety overview, the MAH referred to bibliographic data from the following studies: Reid, 2019; Blasco and Stansbury, 1996; Montgomery, 2016; Bachrach, 1998; Stern, 1997; Zeller, 2012a; Parr, 2017; Mier, 2000; Zeller, 2012b. In these studies, a total of 447 patients (who completed a study) were treated with glycopyrronium bromide.

Adverse events were not recorded systematically across the studies. Based on the available information, the most common adverse events associated with oral glycopyrronium bromide for sialorrhea are typical for anticholinergic medication, e.g. dry mouth, constipation, vomiting and urinary retention.

Patients will be titrated based on tolerance. Section 4.2 of the SmPC advises prior to each increase in dose to review the tolerability of the current dose level. This is acceptable.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rybrila.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Off label treatment of children with mild to moderate sialorrhoea
	• Anticholinergic effects:
	  ○ Constipation
	  ○ Urinary retention
	  ○ Pneumonia

	○ Risk of overheating • Off label use in patients below the age of 3 years due to the higher susceptibility to adverse effects • Overdose, including unintentional overdose due to 15 ml syringe.
Important potential risks	• Cardiac disorders • Dental caries • CNS effects
Missing information	• Safety in long-term use, beyond 24 weeks

Further, additional risk minimisation measures are taken pursuant to Article 21a/22 of Directive 2001/83/EC, which include physician educational material (prescriber checklist) and patient information packs (reminder card).

Educational material in the form of prescriber checklist should be included for the following safety concerns:

- Constipation
- Urinary retention
- Pneumonia
- Risk of overheating
- Overdose including unintentional overdose due to 10 ml syringe
- Cardiac disorders
- Dental caries
- CNS effects
- Off label treatment of children with mild to moderate sialorrhoea
- Off label use in patients below the age of 3 years due to the higher susceptibility to adverse effects
- Safety in long-term use, beyond 24 weeks

Educational material for the patient or patient's carer should be included for the following safety concerns:

- Constipation
- Urinary retention
- Pneumonia
- Risk of overheating
- Overdose including unintentional overdose due to <fill in size> syringe
- Cardiac disorders
- Dental caries
- CNS effects

The corresponding sections of the RMP was requested and has been updated accordingly.

Annex of the RMP

The following should be included in annex 6 of the RMP Details of proposed additional risk minimisation activities (if applicable):

The MAH ensures that in each Member State where Rybrila is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use Rybrila have access to or are provided with the following educational packages:

The physician educational material should contain:

- The Summary of Product Characteristics
- Remarks on the importance of reporting on specific adverse drug reactions, namely: urinary retention, constipation, pneumonia, allergic reactions, dental caries, cardiovascular effects, CNS effect and overheating
- The Prescriber checklist, which shall contain the following key messages:
    a. Information on the administration of Rybrila
    b. Management and minimisation of anticholinergic reactions

The patient information pack should contain:

- Patient information leaflet
- The reminder card for patient's carer, which shall contain the following key messages:
    a. Information on the administration of Rybrila
    b. Management and minimisation of anticholinergic reactions

Drug utilisation study

It was noted that for a previously approved glycopyrronium medicinal product, which was approved through the centralised procedure, a drug utilisation study (DUS) is ongoing with primary objective to monitor and assess the effectiveness of the risk minimisation measures in place, i.e. the product information provided to healthcare professionals and for the patient's carer.

Additionally, as secondary objective the study will monitor;

- The number of anticholinergic adverse events brought to the attention of the prescribing physician (initiator – e.g. consultant neurologist) by the carer that occur in between the routine consultation time interval.
- The number of occasions the treatment is stopped due to anticholinergic adverse events, by type.
- Quantify the frequency of off-label use.
- To collect Quality of Life (QoL) data using Drooling Impact Scale.

This DUS is a category 3 study which started July 2017. End of data collection is December 2022 and Final report of study results is indicated to be June 2023. This is a prospective observational study in five countries and data will be collected via participating prescribers after informed consent of the patient/carer. If the results of this ongoing DUS lead to changes in additional risk minimisation measures (RMM) or routine RMM for this

glycopyrronium medicinal product, this might be relevant for Rybrila and the MAH should consider to implement these as well. The MAH is expected to follow the outcome of this study and to implement any relevant results from this study once requested by regulatory authorities. As the MAH is not expected to join this DUS, a description of the DUS was not required. The MAH has included an adequate description of how effectiveness of the additional risk minimization measures will be evaluated in the RMP.

IV.7 Discussion on the clinical aspects

For this well-established use application, reference was made to clinical studies and experience with the active substance glycopyrronium bromide. No new clinical studies were conducted. The MAH presented an adequate literature overview of glycopyrronium bromide pharmacokinetics, pharmacodynamics, clinical efficacy and clinical safety. The beneficial effect of glycopyrronium bromide in the treatment of excessive drooling in paediatric patients with neurological disorders is considered established. A uncertainty in the beneficial effect is the maintenance of effect, which has not been evaluated in controlled long term studies. This uncertainty is resolved by restricting treatment to short-term intermittent use through the SmPC. Further, the MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the US product Cuvposa.

Risk management is adequately addressed. The safety profile of glycopyrronium bromide is well known. The most common adverse events are typical anticholinergic adverse events, e.g.: dry mouth, constipation, vomiting, drowsiness and urinary retention. Anticholinergic effects are well documented and warnings regarding potential adverse events are adequately reflected in the proposed SmPC. Long term safety has not been evaluated in a controlled setting. This uncertainty is also resolved by restricting treatment to short-term intermittent use.

The SmPC has been aligned as much as possible with that of a previously approved glycopyrronium medicinal product which was approved through the centralised procedure. This was requested by the RMS since from a clinical point of view, this would be in benefit of patients and healthcare professionals.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Glycopyrronium Bromide 1mg/5ml Oral Solution. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rybrila 160 micrograms/ml oral solution is a well-established use medical product and has a proven chemical-pharmaceutical quality. Rybrila is an effective drug, which use is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Rybrila with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 May 2021.

VII. REFERENCES

Abboud, T. K., Read, J., Miller, F., Chen, T., Valle, R., & Henriksen, E. H. (1981). Use of glycopyrrolate in the parturient: effect on the maternal and fetal heart and uterine activity. *Obstetrics and gynecology*, *57*(2), 224–227.

Abboud, T., Raya, J., Sadri, S., Grobler, N., Stine, L., & Miller, F. (1983). Fetal and maternal cardiovascular effects of atropine and glycopyrrolate. *Anesthesia and analgesia*, *62*(4), 426–430.

Bachrach, S. J., Walter, R. S., & Trzcinski, K. (1998). Use of glycopyrrolate and other anticholinergic medications for sialorrhea in children with cerebral palsy. *Clinical pediatrics*, *37*(8), 485–490. https://doi.org/10.1177/000992289803700805

Blasco, P. A., & Stansbury, J. C. (1996). Glycopyrrolate treatment of chronic drooling. *Archives of pediatrics & adolescent medicine*, *150*(9), 932–935. https://doi.org/10.1001/archpedi.1996.02170340046009

Briggs, G.G., Freeman, R.K., Yaffe, S.J. (2011). *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* (9th ed.). Lippincott Williams & Wilkins.

Burger, D. M., Wiestner, T., Hubler, M., Binder, H., Keiser, M., & Arnold, S. (2006). Effect of anticholinergics (atropine, glycopyrrolate) and prokinetics (metoclopramide, cisapride) on gastric motility in beagles and labrador retrievers. *Journal of veterinary medicine. A, Physiology, pathology, clinical medicine*, *53*(2), 97–107. https://doi.org/10.1111/j.1439-0442.2006.00787.x

Carter N. J. (2013). Inhaled glycopyrronium bromide: a review of its use in patients with moderate to severe chronic obstructive pulmonary disease. *Drugs*, *73*(7), 741–753. https://doi.org/10.1007/s40265-013-0058-7

Diaz, D. M., Diaz, S. F., & Marx, G. F. (1980). Cardiovascular effects of glycopyrrolate and belladonna derivatives in obstetric patients. *Bulletin of the New York Academy of Medicine*, *56*(2), 245–248.

Eiland L. S. (2012). Glycopyrrolate for chronic drooling in children. *Clinical therapeutics*, *34*(4), 735–742. https://doi.org/10.1016/j.clinthera.2012.02.026

Franko, B. V., Aplhin, R. S., Ward, J. W., & Lunsford, C. D. (1962). Pharmacodynamic evaluation of glycopyrrolate in animals. *Annals of the New York Academy of Sciences*, *99*, 131–149. https://doi.org/10.1111/j.1749-6632.1962.tb45296.x

Franko, B. V., Ward, J. W., Gilbert, D. L., & Woodard, G. (1970). A condensed format for reporting toxicologic data--results of studies on glycopyrrolate. *Toxicology and applied pharmacology*, *17*(2), 361–365. https://doi.org/10.1016/0041-008x(70)90193-6

ForthTox Limited (2015). In Silico *toxicology consultancy report*. *Toxicological analysis of one structure using Derek Nexus and Leadscope.* 16 July 2015.

Garnock-Jones K. P. (2012). Glycopyrrolate oral solution: for chronic, severe drooling in pediatric patients with neurologic conditions. *Paediatric drugs*, *14*(4), 263–269. https://doi.org/10.2165/11208120-000000000-00000

Haddad, E. B., Patel, H., Keeling, J. E., Yacoub, M. H., Barnes, P. J., & Belvisi, M. G. (1999). Pharmacological characterization of the muscarinic receptor antagonist, glycopyrrolate, in human and guinea-pig airways. *British journal of pharmacology*, *127*(2), 413–420. https://doi.org/10.1038/sj.bjp.0702573

Ishizaki, T., Tawara, K., Oyama, Y., & Nakaya, H. (1978). Clinical pharmacologic observations on timolol. II. Antihypertensive effect and kinetic disposition on twice-daily dosing in patients with mild or moderate hypertension. *Journal of clinical pharmacology*, *18*(11-12), 519–529. https://doi.org/10.1002/j.1552-4604.1978.tb01581.x

Kagiwada, K., Ishizaki, T., Saito, G. (1973). Effects of the anticholinergic agent Glycopyrrolate on foetal development and neonatal growth in mice and rats. *Oyoyakuri* (Pharmacometrics) *18*(5), 617-626.

Kaltiala, E., Penttilä, A., Vapaatalo, H., & Larmi, T. (1974). The fate of intravenous (3H)glycopyrrolate in man. *The Journal of pharmacy and pharmacology*, *26*(5), 352–354. https://doi.org/10.1111/j.2042-7158.1974.tb09287.x

MHRA. (2019). *Interactive Drug Analysis Profile for glycopyrronium.*

Mier, R. J., Bachrach, S. J., Lakin, R. C., Barker, T., Childs, J., & Moran, M. (2000). Treatment of sialorrhea with glycopyrrolate: A double-blind, dose-ranging study. *Archives of pediatrics & adolescent medicine*, *154*(12), 1214–1218. https://doi.org/10.1001/archpedi.154.12.1214
Mirakhur, R. K., Dundee, J. W., & Jones, C. J. (1978). Evaluation of the anticholinergic actions of glycopyrronium bromide. *British journal of clinical pharmacology*, *5*(1), 77–84. https://doi.org/10.1111/j.1365-2125.1978.tb01601.x

Mirakhur, R. K., & Dundee, J. W. (1983). Glycopyrrolate: pharmacology and clinical use. *Anaesthesia*, *38*(12), 1195-1204.

Montgomery, J., McCusker, S., Lang, K., Grosse, S., Mace, A., Lumley, R., & Kubba, H. (2016). Managing children with sialorrhoea (drooling): Experience from the first 301 children in our saliva control clinic. *International journal of pediatric otorhinolaryngology*, *85*, 33–39. https://doi.org/10.1016/j.ijporl.2016.03.010

Nair, A. B., & Jacob, S. (2016). A simple practice guide for dose conversion between animals and human. *Journal of basic and clinical pharmacy*, *7*(2), 27–31. https://doi.org/10.4103/0976-0105.177703

Ogoda, M., Niiya, R., Koshika, T., & Yamada, S. (2011). Comparative characterization of lung muscarinic receptor binding after intratracheal administration of tiotropium, ipratropium, and glycopyrrolate. *Journal of pharmacological sciences*, *115*(3), 374-382.

Parr, J. R., Todhunter, E., Pennington, L., Stocken, D., Cadwgan, J., O'Hare, A. E., Tuffrey, C., Williams, J., Cole, M., & Colver, A. F. (2018). Drooling Reduction Intervention randomised trial (DRI): comparing the efficacy and acceptability of hyoscine patches and glycopyrronium liquid on drooling in children with neurodisability. *Archives of disease in childhood*, *103*(4), 371–376. https://doi.org/10.1136/archdischild-2017-313763

Proakis, A. G., & Harris, G. B. (1978). Comparative penetration of glycopyrrolate and atropine across the blood--brain and placental barriers in anesthetized dogs. *Anesthesiology*, *48*(5), 339–344. https://doi.org/10.1097/00000542-197805000-00007

Pulido-Rios, M. T., McNamara, A., Obedencio, G. P., Ji, Y., Jaw-Tsai, S., Martin, W. J., & Hegde, S. S. (2013). In vivo pharmacological characterization of TD-4208, a novel lung-selective inhaled muscarinic antagonist with sustained bronchoprotective effect in experimental animal models. *The Journal of pharmacology and experimental therapeutics*, *346*(2), 241–250. https://doi.org/10.1124/jpet.113.203554

Rautakorpi, P., Ali-Melkkilä, T., Kaila, T., Olkkola, K. T., Iisalo, E., Iisalo, E., & Kanto, J. (1994). Pharmacokinetics of glycopyrrolate in children. *Journal of clinical anesthesia*, *6*(3), 217–220. https://doi.org/10.1016/0952-8180(94)90062-0

Rautakorpi, P., Manner, T., Ali-Melkkilä, T., Kaila, T., Olkkola, K., & Kanto, J. (1998). Pharmacokinetics and oral bioavailability of glycopyrrolate in children. *Pharmacology & toxicology*, *83*(3), 132–134. https://doi.org/10.1111/j.1600-0773.1998.tb01456.x

Reid, S. M., Westbury, C., Guzys, A. T., & Reddihough, D. S. (2020). Anticholinergic medications for reducing drooling in children with developmental disability. *Developmental Medicine & Child Neurology*, *62*(3), 346-353.

Roper, R. E., & Salem, M. G. (1981). Effects of glycopyrrolate and atropine combined with antacid on gastric acidity. *British journal of anaesthesia*, *53*(12), 1277–1280. https://doi.org/10.1093/bja/53.12.1277

Roush, J. K., Keene, B. W., Eicker, S. W., & Bjorling, D. E. (1990). Effects of atropine and glycopyrrolate on esophageal, gastric, and tracheal pH in anesthetized dogs. *Veterinary surgery : VS*, *19*(1), 88–92. https://doi.org/10.1111/j.1532-950x.1990.tb01147.x

Rumpler, M. J., Sams, R. A., & Colahan, P. (2011). Pharmacokinetics of glycopyrrolate following intravenous administration in the horse. *Journal of veterinary pharmacology and therapeutics*, *34*(6), 605–608. https://doi.org/10.1111/j.1365-2885.2011.01272.x

Rumpler, M. J., Kandala, B., Vickroy, T. W., Hochhaus, G., & Sams, R. A. (2014). Pharmacokinetics and pharmacodynamics of glycopyrrolate following a continuous-rate infusion in the horse. *Journal of veterinary pharmacology and therapeutics*, *37*(2), 133–144. https://doi.org/10.1111/jvp.12074

Saito, G., Amemiya, K., Suzuki, H., Kudo, M., Saga, K., Kato, M., and Kagiwada, K. (1973). A study of toxicity of the anticholinergic agent Glycopyrrolate (Report 1). Acute toxicity, and, in rats, subacute and chronic toxicity. *Oyoyakuri [Pharmacometrics], 7*(5), 627-653.

Santus, P., Radovanovic, D., Cristiano, A., Valenti, V., & Rizzi, M. (2017). Role of nebulized glycopyrrolate in the treatment of chronic obstructive pulmonary disease. *Drug design, development and therapy*, *11*, 3257–3271. https://doi.org/10.2147/DDDT.S135377

Stern, L. M. (1997). Preliminary study of glycopyrrolate in the management of drooling. *Journal of paediatrics and child health*, *33*(1), 52-54.

Sykes, D. A., Dowling, M. R., Leighton-Davies, J., Kent, T. C., Fawcett, L., Renard, E., ... & Charlton, S. J. (2012). The influence of receptor kinetics on the onset and duration of action and the therapeutic index of NVA237 and tiotropium. *Journal of Pharmacology and Experimental Therapeutics*, *343*(2), 520-528.

Villetti, G., Bergamaschi, M., Bassani, F., Bolzoni, P. T., Harrison, S., Gigli, P. M., Janni, A., Geppetti, P., Civelli, M., & Patacchini, R. (2006). Pharmacological assessment of the duration of action of glycopyrrolate vs tiotropium and ipratropium in guinea-pig and human airways. *British journal of pharmacology*, *148*(3), 291–298. https://doi.org/10.1038/sj.bjp.0706724

Zeller, R. S., Davidson, J., Lee, H. M., & Cavanaugh, P. F. (2012a). Safety and efficacy of glycopyrrolate oral solution for management of pathologic drooling in pediatric patients with cerebral palsy and other neurologic conditions. *Therapeutics and clinical risk management*, *8*, 25–32. https://doi.org/10.2147/TCRM.S27362

Zeller, R. S., Lee, H. M., Cavanaugh, P. F., & Davidson, J. (2012b). Randomized Phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions. *Therapeutics and clinical risk management*, *8*, 15–23. https://doi.org/10.2147/TCRM.S26893

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse