21 July 2016
EMA/555265/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Sialanar

International non-proprietary name: glycopyrronium bromide

Procedure No. EMEA/H/C/003883/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
**Send a question via our website** www.ema.europa.eu/contact

# Table of contents

# List of abbreviations

| | |
|---|---|
| Ach | acetylcholine |
| ADI | acceptable daily intake |
| ADRs | adverse drug reactions |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AP | Applicant's Part (or Open Part) of a ASMF |
| API | Active Pharmaceutical Ingredient |
| APPM | Association of Paediatric Palliative Medicine Master Formulary |
| AR | Assessment Report |
| ASM | Active Substance Manufacturer |
| ASMF | Active Substance Master File (Drug Master File) |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | area under the time-concentration curve |
| $AUC_{(0-t)}$ | area under the plasma concentration vs. time curve, from time zero to t, where t was the last quantifiable concentration |
| $AUC_{(0-\alpha)}$ | area under the plasma concentration vs. time curve, with extrapolation to infinity |
| BA | bioavailability |
| BE | bioequivalence |
| BMI | Body Mass Index |
| BNFc | British National Formulary for Children |
| BP | British Pharmacopoeia or blood pressure |
| bpm | beats per minute |
| CE | Conformité Européene |
| CEP | Certificate of Suitability of the Ph.Eur. |
| CHMP | Committee for Medicinal Products for Human Use |
| CHO | chinese hamster ovary |
| $C_{max}$ | maximum concentration in plasma (or serum) |
| CI | confidence interval |
| Cl | (total plasma) clearance |
| CMS | Concerned Member State |
| CNS | central nervous system |
| CoA | Certificate of Analysis |
| CP | cerebral palsy |
| CRS | Chemical Reference Substance (official standard) |
| CSF | cerebrospinal fluid |
| CSR | clinical study report |
| %CV | intra-subject coefficient of variation |
| DAP | Drug Approval Package (FDA) |
| DMF | Drug Master File (active substance master file) |
| DP | Decentralised (Application) Procedure |
| EC | European Commission |
| $EC_{50}$ | Effective concentration 50% |
| ECG | electrocardiogram |

| | |
|---|---|
| EDQM | European Directorate for the Quality of Medicines |
| EMA | European Medicines Agency |
| ESI | Electro Spray Ionisation |
| EU | European Union |
| F | bioavailability |
| FDA | Food and Drug Administration (United States) |
| GB | glycopyrronium bromide |
| GBOS | glycopyrronium bromide oral solution |
| GC | gas chromatography |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| GP | glycopyrronium |
| H | hour(s) |
| HDPE | high density polyethylene |
| HPLC | high performance liquid chromatography |
| HR | heart rate |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| i.m. | intramuscular(ly) |
| IU | International Units |
| IPC | in-process control |
| IR | Infrared |
| i.v. | intravenous(ly) |
| kg | kilogram(s) |
| λz | terminal elimination rate constant |
| L | litre(s) |
| $LD_{50}$ | lethal dose 50% |
| LDPE | low density polyethylene |
| LLOQ | Lower Limit of Quantification |
| LoA | Letter of Access |
| LOD | loss on drying |
| LoD | limit of detection |
| LoQ | limit of quantitation |
| M | muscarinic (receptor) |
| MA | Marketing Authorisation |
| MAA | Marketing Authorisation Application |
| MAH | Marketing Authorisation Holder |
| mBMRS | Modified Behavioural and Medical Rating Scale |
| mg | milligram(s) |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| mL | millilitre(s) |
| min | minute(s) |
| mITT | Modified Intended to Treat |

| | |
|---|---|
| mM | millimolar |
| MoA | mechanism of action |
| MS | Mass Spectrometry |
| µg | microgram |
| mTDS | Modified Teacher's Drooling Scale |
| NICE | National Institute for Health and Care Excellence |
| TEAE | treatment-emergent adverse event |
| ND | not detected |
| NDA | New Drug Application |
| NHS | National Health Service |
| NLT | not less than |
| NMR | Nuclear Magnetic Resonance |
| NMT | not more than |
| NOEL | no effect level |
| NS | not significant |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OOS | Out of Specification |
| OTC | over-the-counter |
| PAH | Pulmonary Arterial Hypertension |
| P/C | parent(s)/caregiver |
| PCA | prescription cost analysis data |
| PD | pharmacodynamics |
| PD | Parkinson disease |
| $PD_{50}$ | preventive dose 50% |
| PDCO | Paediatric Committee |
| PDE | permitted daily exposure |
| pg | picogram |
| Ph. Eur. | European Pharmacopoeia |
| PhV | PharmacoVigilance |
| PI | Prescribing Information (United States) |
| PL/PIL | Package Leaflet |
| PIP | Paediatric Investigational Plan |
| PK | pharmacokinetics |
| PUMA | Paediatric Use Marketing Authorisation |
| QC | quality control |
| QoL | quality of life |
| QOS | quality overall summary |
| RH | relative humidity |
| RMS | Reference Member State |
| RP | Restricted Part (or Closed Part) of a ASMF |
| RRT | relative retention time |
| RSD | relative standard deviation |
| SA | sino-atrial |
| s.c. | Subcutaneous(ly) |
| SD | standard deviation |
| SmPC | Summary of Product Characteristics |

| | |
|---|---|
| SOP | Standard Operating Procedure |
| t | time |
| $t_{½}$ | half-life |
| $t_{½z}$ | apparent terminal elimination half-life |
| TEAE | treatment-emergent adverse event |
| t.i.d | three times daily |
| $T_{max}$ | time to maximum observed plasma concentration |
| TSE | transmissible spongiform encephalopathies |
| UK | United Kingdom |
| ULN | upper limit of the normal range |
| USP/NF | United States Pharmacopoeia/National Formulary |
| US | United States |
| UV | Ultraviolet |
| VAS | visual analogue scale |
| $V_{ß}$ | volume of distribution in the elimination phase |
| $V_{ss}$ | volume of distribution at steady state |
| WEU | Well Established Use |
| XRD | X-Ray Diffraction |
| µCi | microcurie |
| µM | micromolar |

*Not all abbreviations may be used.

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Proveca Limited submitted on 28 November 2014 an application for a Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Sialanar, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 October 2013.

The applicant applied for the following indication:

Treatment of sialorrhoea (chronic pathological drooling) in children aged 2 to <18 years with neurological disorders.

**The legal basis for this application refers to:**

Article 10(a) of Directive 2001/83/EC – relating to applications relying on well-established medicinal use supported by bibliographic literature.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on bibliographic literature substituting non-clinical tests and clinical studies.

***Information on Paediatric requirements***

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0240/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0240/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0240/2014.

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

***Scientific Advice***

The applicant received Scientific Advice from the CHMP on 15 March 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

***Licensing status***

The product was not licensed in any country at the time of submission of the application.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Heisterberg Co-Rapporteur: Radka Montoniová

- The application was received by the EMA on 28 November 2014.
- The procedure started on 26 February 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 May 2015.
- PRAC RMP assessment overview adopted by PRAC on 11 June 2015.
- During the meeting on 25 June 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2015.
- PRAC RMP assessment overview adopted by PRAC on 4 December 2016.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 2 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List outstanding issues to all CHMP members on 11 March 2016.
- PRAC RMP assessment overview adopted by PRAC on 17 March 2016.
- During the CHMP meeting on 31 March 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Sialanar.

### *1.3. Steps taken for the re-examination procedure*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Arantxa Sancho Lopez

- The applicant submitted written notice to the EMA on 4 May 2016 to request a re-examination of Sialanar CHMP opinion of 28 April 2016.
- The Committee appointed Kristina Dunder as re-examination Rapporteur and Arantxa Sancho Lopez as the re-examination Co-Rapporteur by written procedure on 17 May 2016.
- The applicant submitted the detailed grounds for the re-examination on 23 May 2016. The re-examination procedure started on 24 May 2016.
- The rapporteur's re-examination assessment report was circulated to all CHMP members on 21 June 2016. The co-rapporteur's assessment report was circulated to all CHMP members on 23 June 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 30 June 2016.
- During a meeting of the SAG on 11 July 2016, experts were convened to consider the grounds for re-examination.
- During the CHMP meeting on 19 July 2016, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21 July 2016, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the marketing authorisation.

# 2. Scientific discussion

## *2.1. Introduction*

### Problem statement

Sialorrhoea or drooling is the unintentional loss of saliva from the mouth and is a normal phenomenon in infancy. As neurological control of the tongue and bulbar musculature develops, excessive drooling normally stops around the age of 15-18 months of age. However, a high number of developing children will continue to drool until 3 years of age, especially during periods of eating or drinking (Mier et al 2000). Drooling beyond the age of 4 years of age is considered neurodevelopmentally abnormal (Fairhurst and Cockerill 2011).

The diagnosis of sialorrhoea before 2 years of age is inappropriate, irrespective of the presence of an underlying neurological disorder. Most children in this age group would be more appropriately treated with a less invasive behavioural approach, at least initially.

Pathological drooling is common in children and adults with CP, but most frequently in individuals who are also developmentally disabled. Other rarer and often more debilitating neurological disorders and neurodegenerative diseases can also be associated with sialorrhoea, including amyotrophic lateral sclerosis,

Rett syndrome, Angelman syndrome, and epilepsy. The risk for occurrence and/or increased severity of drooling in any child with a neurological disorder can be made worse by several concomitant medications commonly administered in these populations including anticonvulsants such as clobazam and clonazepam and neuroleptic drugs.

The pathophysiology of sialorrhoea is not clear. However, the following five factors have an impact on the complex and coordinated process of swallowing and are thought to contribute in varying degrees to drooling in individuals with neurological disorders (Blasco 1992; Mier 2000):

- Integrity of oral structures;
- Oropharyngeal motor function;
- Orofacial sensory perception and feedback;
- Rate of saliva secretion; and
- Cognitive awareness of salivary spill.

Saliva production and swallowing is an automatic act. However, it is dependent on the ability to feel the build-up of saliva within the mouth and relies upon the normal movement of the tongue to collect it and transfer it to the back of the mouth for swallowing. A child will typically produce 1-1.5 liters of salvia everyday with the production predominantly occurring in three pairs of salivary glands: the submandibular, sublingual and parotid. The submandibular glands account for 65-70% of unstimulated production of saliva so are the primary source of saliva in sialorrhoea (Fairhurst 2011, Erasmus 2009).

Uncontrolled sialorrhoea can have negative consequences for health and quality of life (QoL) (Parr, 2014; Fairhurst, 2011; Mier, 2000; Harris, 1987; Hockstein, 2004; Van De Heyning, 1980; Van der Burg, 2006). Detrimental effects may include:

- Irritated and macerated skin
- Dehydration
- Constant wetness and foul odour of clothing
- Interference with interpersonal relationships, e.g. poor speech intelligibility restricting communication between child and parent
- Lowering of self-esteem
- Restricted vocational options

In addition to these external manifestations of drooling, children with the most severe pharyngeal dysphagia are at medical risk due to saliva aspiration to the lungs, which can lead to recurrent episodes of pneumonia (Erasmus, 2012).

Several non-invasive options are available as a first-line management of sialorrhoea (directed at the cause), such as practical aids, speech therapy, physiotherapy.

Further therapeutic options of increasing invasiveness exist, such as anticholinergic medication, botulinum toxin or surgical removal or ligation of some of the salivary glands.

At present, there is insufficient evidence to be able to distinguish between these different approaches, though it is clear that none of them is completely successful in all individuals. Currently, the most comprehensive

management guidelines for the treatment of sialorrhoea are those that were published by UK clinicians in 2011 (Fairhurst 2011). In these guidelines each of the available treatment options was reviewed including glycopyrronium bromide, hyoscine patches and benzhexol. These guidelines are supplemented by recently published UK paediatric formularies, including the standard reference book Paediatric Palliative Medicine (2010) (Hain, 2010) and 2012 edition of the Association of Paediatric Palliative Medicine (APPM) Master Formulary (APPM, 2012) both recommend GP for the management of sialorrhoea. Furthermore, GP is included in expert recommendations (Erasmus, 2012) in the Netherlands as a treatment option for individuals with CP requiring drooling control who are not suitable for botulinum toxin therapy or surgery.

Drug therapy is aimed at decreasing the volume of saliva without addressing impaired swallowing. Historically, a range of drugs with anticholinergic (antimuscarinic) actions have been used in an attempt to control sialorrhoea.

Anticholinergic drugs work by decreasing the volume of saliva secreted from the salivary glands and thus the severity of drooling. Hyoscine (scopolamine), benztropine mesylate and benzhexol have all been shown to be useful for controlling drooling in children with neurological disorders. However, their lack of selectivity leads to widespread, undesirable, and often poorly tolerated central and peripheral effects, including restlessness, irritability, drowsiness, constipation, urinary retention, and flushing.

GP is a quaternary ammonium member of the anticholinergic class of drugs, which has been demonstrated to be effective in reducing sialorrhoea. As a consequence of its quaternary charge, GP has limited ability to penetrate the blood brain barrier. Therefore, there is an widely held belief that, compared with other anticholinergic drugs, children treated with GP will exhibit a better tolerated safety profile, though the results of a clinical study (Parr, 2014) investigating this possibility have yet to be reported.

There are currently no approved products in EU for the treatment of excessive drooling (sialorrhoea). However, in the European Union, several different anticholinergic drugs are commonly used off-label for the pharmacological treatment of sialorrhoea including atropine and, especially, GP and hyoscine. Dosing of GP is by body weight (mg/kg) using a dose titration scheme. The total daily dose in clinical practice is reported to be in the range 0.06 - 0.3 g/kg/day, often split into 2 to 3 doses (Proveca, 2012). For hyoscine patches dose adjustment is often achieved by cutting up and applying only part of a patch for 72 hours. This can result in leakage of drug, giving a high dose in the first day and little drug for the following 48 hours.

The absence of a paediatric-appropriate formulation licensed for the treatment of sialorrhoea currently represents an impediment to effective treatment of this distressing condition.

## About the product

Glycopyrronium bromide is a water-soluble synthetic quaternary amine. It is a peripheral antimuscarinic (anticholinergic) agent. GP acts as a competitive antagonist at muscarinic receptors in the autonomic nervous system. One of the pharmacological actions of all anticholinergic drugs is the reduction of secretions through antagonism of cholinergic M3 stimulation (Tscheng et al. 2002). GP, administered via the intravenous (i.v.), intramuscular (i.m.), and oral routes, has been shown to reduce salivary secretions in healthy adult volunteers (Mirakhur, 1978a; Mirakhur, 1980) and surgical patients (Mirakhur, 1979b; Ali-Melkkilä, 1989; Ali-Melkkilä, 1990a). Compared with atropine, GP is selective and 6-times more potent with a longer duration of effect on salivary secretions.

Glycopyrronium bromide has affinity at all five human muscarinic acetylcholine (ACh) receptor subtypes (Ki = 0.15 – 2.0 nM) in order M1 > M3 > M2/M4 > M5. GP is 2-4 times more selective for the M3 and M1 subtypes than M2, making it one of the most potent M3 blockers available (Bird et al. 2011).

The applied dose is based on the weight of the child, starting with approximately 0.02 mg/kg per dose, three times per day and increasing by 0.02 mg/kg per dose every 7 days. Dose titration should be continued until efficacy is balanced with side effects and amended up or down as appropriate, to a maximum individual dose of 7.5 ml (3.0 mg) three times a day.

The applied indication is:

Treatment of sialorrhoea (chronic pathological drooling) in children aged 2 to <18 years with neurological disorders.

## Type of Application and aspects on development

Sialanar is submitted as a Paediatric Use Marketing Authorisation (PUMA) (Article 31 of Regulation (EC) No 1901/2006) under Article 10a (well-established use) of Directive 2001/83/EC (as amended) via the centralised procedure.

In accordance with Article 10a of Directive 2001/83/EC the application shall rely on appropriate scientific literature substituting non-clinical tests and clinical studies if it can be demonstrated that the active substance of a medicinal product has been in well-established medicinal use within the European Union for at least 10 years**,** with a recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I (Part II.1) to Directive 2001/83/EC shall apply.

The requirements, described in Article 10a read in combination with the abovementioned Annex I, are discussed below:

***- Time over which the substance has been used and quantitative aspects of use of the substance***

For an application under article 10a of Directive 2001/83/EC, it must be established that the substance has been in well-established medicinal use for at least 10 years in the Union, with a “recognised efficacy and an acceptable level of safety” in the applied indication.

It appears that the use of the substance in the European Union in the applied indication has been extremely limited, except in the United Kingdom where the applicant provided the following evidence of use. It has been included in the British National Formulary for Children (BNFc) for the past 10 years. Direct evidence from prescription cost analysis (PCA) data for 15 years and feedback from individual prescribers to support its use for longer than 10 years within the UK in the claimed indication was submitted. A survey by Parr et al in 2012 indicated that GP is prescribed by 70% of all consultant paediatricians with an interest in neurodisability in the UK.

The Applicant’s own survey (Proveca, 2012) provided figures of current and anticipated usage in a sample of prescribers in the UK. 37 of 636 (6%) patients with drooling, in the care of those surveyed were prescribed GP. The Proveca survey also showed usage in the Netherlands and Ireland. The data from the survey conducted by the applicant, while contributing some relevant information, are of limited value due to a small sample size and the methodology used.

The fact that GP has been included in prescribing texts, including the British National Formulary for Children, for more than 10 years is not considered as evidence of systematic and documented use for at least 10 years as it does not document the actual use in the indication applied for.

The PCA prescription data do not include information on the indication therefore they do not allow demonstration of the quantitative use. The unlicensed uses of GP are known to be sialorrhoea, drying of respiratory secretions and hyperhidrosis, although the use in hyperhidrosis is topical and is captured separately. Hence, the PCA data on the GP use as presented by the Applicant include both sialorrhoea and drying of respiratory secretions.

The surveys conducted by Parr and by the Applicant indicated that the physicians targeted in the surveys have prescribed GP for pathological drooling in children for many years, but the actual numbers of prescriptions from the PCA database are very low from 1999 to 2006 (less than 200 items dispensed annually in England).

However the applicant was able to show considerably higher prescriptions numbers for drooling or related disorders calculated from the UK database Clinical Practice Research Datalink (CPRD) giving detailed information such as age, diagnoses, medical history and medication history. This database only encompasses about 6.9% of UK prescribing. 115 children with a specific diagnosis of drooling and 313 children with conditions indicative of drooling could be identified.

Based on these 428 children identified annual prescriptions of glycopyrronium in children for drooling in the UK as ranging from 2388 in year 2006 to 22804 in year 2015 were calculated (community prescribing only; no hospital prescribing).

Although a firm diagnosis of drooling has been established in only 115 children in the CPRD database, it is accepted that the detailed medical history available from this database allows establishing with sufficient certainty a diagnosis of drooling in additional 313 children.

These 313 children suffered from neurological disorders, which together with their use of glycopyrronium and the absence of other conditions where anticholinergic medicines may be used, make a diagnosis of drooling sufficiently likely. Hence, it is supported that 428 children from the CPRD database have been treated with glycopyrronium for pathological drooling due to neurological disorders in the period 2006-2015. When taking into account the prevalence of the condition, this is considered sufficient to meet the quantitative requirements for well-established in the EU.

Importantly to give assurance that the prescription numbers are representative for UK-wide prescribing and not produced by some heavy prescribers, the Applicant could show that none of the physicians participating in the CPRD and prescribing glycopyrronium for drooling were prescribing to more than 5 patients.

Of those practices that prescribed glycopyrronium for drooling, most prescriptions were to single patients. 60 practices prescribed to 2 patients by practice with a few prescribing to 3 or 4 patients. Rarely practices prescribed to 5 patients and none prescribed to more than 5 patients. It has also been shown that the few practices prescribing to 5 patients only had a minor impact on the total number of prescriptions.

When taking into account the prevalence of the condition, the number of prescriptions described in the CPRD database is considered sufficient to meet the criterion of the time over which the substance has been used and the quantitative aspects of the use of the substance. This could be further substantiated by the applicant, who showed that the prescription numbers were representative for UK-wide prescribing and not produced by a view heavy prescriber.

***- The degree of scientific interest in the use of the substance***

The Applicant provided a comprehensive overview of the literature published from the early 1990s to the present day where glycopyrronium is mentioned, discussed or investigated in the context of the proposed indication or related uses. Whereas the provided 21 publications over 23 years world-wide have some limitations as most of them were non-European, or did not provide detailed information of glycopyrronium the Applicant gave proof (through EudraCT numbers and an abstract intended to be presented at the Annual Conference of the Royal College of Paediatrics and Child Health) of two clinical studies: a double-blind, randomised placebo-controlled study investigating an oral solution of glycopyrronium in children with hypersalivation associated with neurodevelopmental disability ongoing in Slovakia and Czech Republic and a single-blind study comparing an oral solution of glycopyrronium with a hyoscine cutaneous patch in drooling in children with neurodisability performed in the UK.

Whilst these studies are not yet available in the published literature and do not provide detailed safety and efficacy information, they provide valuable information on current clinical development of this active substance in the claimed indication. Overall, the submitted references above described are considered sufficient evidence of scientific interest in the EU.

***- Coherence of scientific assessments***

The Applicant provided an overview of the publications in which – according to the Applicant – a reference to the use of glycopyrronium for the treatment of pathological drooling in children is made. Most of the publications address pathological drooling in children with neurological disorders and are consistent in their conclusions.

The references are quite heterogeneous, ranging from brief references in a textbook to reports of randomised clinical trials. However, overall, the reports are sufficiently consistent in outlining the effect of glycopyrronium in pathological drooling in children, and therefore it is considered that the coherence of the scientific assessments has been shown.

As a conclusion of the assessment of the above criteria, the CHMP is of the view that the applicant provides sufficient evidence to establish that the elements related to the quantitative aspects of the use of the substance, the time over which the substance has been used, the degree of scientific interest in the use of the substance in the EU and the coherence of the scientific assessments are fulfilled.

***- Similarity of the formulations from the literature***

Two main studies contributing to short and long term efficacy and safety (Zeller at al. 2012a and Zeller at al. 2012b) were performed with a similar formulations and posologies resembling the posology proposed by the Applicant. Bioequivalence has not been established between these formulations/preparations but the recommended initial dose and dose titration schedule has been revised taking into account the higher bioavailability of Sialanar. With the revision of the proposed dose recommendations, it is reasonable to conclude that formulations can be considered sufficiently similar to conclude that the results of the Zeller studies can be applied to Sialanar.

***- Recognised efficacy and acceptable level of safety***

As clarified in sections 2.5 and 2.6, whilst some efficacy of the substance in the claimed indication is recognised despite limitations of the data, the lack of sufficient and reliable qualitative and quantitative data and subsequent resulting uncertainties do not allow establishing that glycopyrronium bromide has been used in the European Union for the symptomatic treatment of sialorrhoea (chronic pathological drooling) in

children and adolescents aged 3 to <18 years with neurological disorders with an acceptable level of safety. The application falls therefore short of demonstrating that the requirements of Article 10a of Directive 2001/83/EC are fulfilled.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as an oral solution containing 400 µg/ml of glycopyrronium bromide (equivalent to 320 µg/ml glycopyrronium) as active substance.

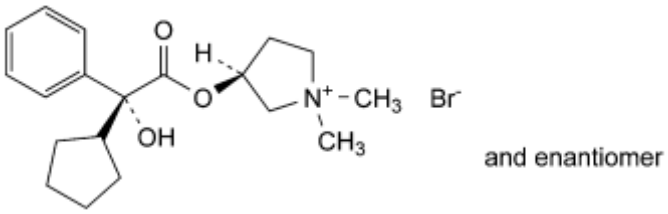
Other ingredients are sodium benzoate (E211), raspberry flavouring (containing propylene glycol E1520), sucralose (E955), citric acid (E330) and purified water.

The product is available in amber coloured glass bottles with a high density polyethylene (HDPE) tamper evident child resistant closures and expanded low density polyethylene (LDPE) liners as described in section 6.5 of the SmPC. Each pack also contains a LDPE oral syringe and syringe adaptor.

### 2.2.2. Active Substance

***General information***

The chemical name of glycopyrronium bromide is (1,1-dimethylpyrrolidin-1-ium-3-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetate bromide corresponding to the molecular formula $C_{19}H_{28}BrNO_3$ and a relative molecular mass of 398.3 g/mol. It has the following structure:




and enantiomer

The active substance is a white to almost white crystalline solid, freely soluble in water and soluble in ethanol. The aqueous solubility is sufficiently high to ensure complete dissolution in the commercial formulation.

Glycopyrronium bromide exhibits stereoisomerism due to the presence of 2 chiral centres. The active substance is a racemic mixture of 3*S*,2*R* and 3*R*,2*S* enantiomers. The diastereomers are controlled in the specification according to the Ph. Eur. monograph.

As there is a monograph of glycopyrronium bromide in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

***Manufacture, characterisation and process controls***

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

***Specification***

The active substance specification includes tests for appearance, solubility, identity, appearance of solution, acidity or alkalinity, loss on drying, sulphated ash, impurities and assay in line with the Ph. Eur. monograph. Additional tests for related substances and solvents (both GC) are also included in the CEP and have been appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for assay testing has been presented.

Certificates of analysis for three batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

***Stability***

Stability data on four production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH), on four different batches for up to 36 months under intermediate conditions (30 ºC / 65% RH), and on one batch for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: identity; description; impurities; loss on drying; assay; melting point. Testing was conducted in accordance with GMP, using Ph. Eur. methods. No significant changes to any of the measured parameters were observed and all parameters remained within specification throughout the studies.

Photostability testing following the ICH guideline Q1B was performed on one batch. No increase in impurities was observed and the assay remained constant, indicating that glycopyrronium bromide is not photosensitive.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months without specific storage conditions in the proposed container.

## 2.2.3. Finished Medicinal Product

***Description of the product and pharmaceutical development***

The finished product is an oral solution aimed at a paediatric population. As such, the formulation development is in line with recommendations given by PDCO during PIP assessment. It is a smooth liquid with a sweet flavour in order to ensure acceptability in paediatric patients and compliance with the posology. The formulation was designed to be simple with no unnecessary excipients. A preservative is required as the product is stored in a multi-dose bottle which will be opened frequently over the likely duration of treatment (up to 24 weeks). Of the preservatives investigated, sodium benzoate was found to work best and meets the requirements of Ph. Eur. 5.1.3 (Efficacy of Microbial Preservation (PET)). The amount added is justified by being well below the acceptable daily intake level and effective in stability studies. Citric acid is also added as an acidifying agent.

Glycopyrronium bromide is highly soluble in water but has a bitter taste which is counteracted by inclusion of a sweetener and flavouring agent in the formulation. Various formulations were made with different sweeteners and flavourings and tested for palatability. Sucralose and raspberry flavour were chosen as the

best options, and their levels set at optimum levels. The acceptability of the final formulation was tested using an E-tongue and in adult clinical trials.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or in-house standards (raspberry flavour). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. Compatibility of the active substance with the excipients was demonstrated in binary mixtures stored at elevated temperature. The formulation used during clinical studies is the same as that intended for marketing.

The finished product was shown to be compatible with a range nasogastric feeding tubes required by some patients. It is non-viscous and thus, complete clearance of glycopyrronium bromide can be achieved with a single 10 ml water rinse.

The primary packaging is an amber coloured glass bottle with HDPE tamper evident child resistant closure and expanded LDPE liner as described in section 6.5 of the SmPC. Each pack also contains a LDPE oral syringe and syringe adaptor, for which CE mark certificates have been provided. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Originally, the applicant proposed a 5 ml syringe and demonstrated compliance with Ph. Eur. 2.9.27 (Uniformity of Mass of Delivered Doses from Multidose Containers). At the request of CHMP and in order to accommodate the highest 6 ml dose of Sialanar, this was replaced with an 8 ml syringe. The applicant committed to demonstrating that the larger syringe complies with Ph. Eur. 2.9.27 by end of June 2016.

***Manufacture of the product and process controls***

The manufacturing process consists of two main steps: dissolution of the active substance and excipients in water followed by filling into bottles. The process is considered to be a standard manufacturing process. Sufficient details have been provided in terms of manufacturing parameters and in-process controls consist of pH checks before and after excipient addition.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this simple compounding process.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form consisting of tests for appearance, identification (HPLC, UV), assay (HPLC), impurities (HPLC), pH (Ph. Eur.), microbial limits (Ph. Eur.), identification and assay of sodium benzoate (HPLC) and fill volume (as IPC).

Appropriate limits for impurities and pH were introduced during the procedure in response to a major objection raised by CHMP. The level of impurity J is below the qualification threshold according to ICH Q3B.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for two production scale batches and one pilot scale batch confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

***Stability of the product***

Stability data on two production scale batches and one pilot scale batch of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH), for up to 24 months under intermediate conditions (30 ºC / 65% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches of Sialanar are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. A stability study on a third production scale batch of Sialanar will be carried out once after the next manufacturing campaign. Samples were subjected to the same tests as for release. The analytical procedures used are stability indicating. No significant trends to any of the measured parameters were observed, other than an increase in one impurity which was more marked at higher temperatures.

Initially, studies demonstrating compatibility with the packaging materials when stored upside down were absent. These studies have now been initiated and early results indicate no leachables or increased instability which suggests no issue with the container closure system. These studies will be continued and any adverse findings reported and addressed post-authorisation.

In addition, one batch stored in the planned commercial amber bottles or in clear glass bottles was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that the finished product is not photosensitive in either format and no storage precautions regarding light are required.

An in-use stability study on one batch of finished product was carried out over a period of four weeks. No significant changes to any of the measured parameters were observed and an in-use shelf life of 28 days is acceptable. A further in-use stability study on a second batch towards the end of its shelf-life will be carried out in line with the guideline on In-Use Stability Testing of Human Medicinal Products in due course.

Based on available stability data, the proposed shelf life of 24 months and without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.2.6. Recommendations for future quality development

The CHMP recommends the following points for investigation:

- The Applicant should repeat the multidose container test on the 8 ml device, testing at 3 dosing volumes 0.6 ml (minimum dose), 2.8 ml (mid-point dose) and 6.0 ml (maximum dose).
- The Applicant should conduct an extended in-use study for up to two months on a batch of finished product towards the end of its shelf life.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

No new non-clinical studies were submitted for the current application, which presents a summary of published literature (17 references) on the pharmacology, pharmacokinetics and toxicology of glycopyrronium bromide in animal species. All ingredients to be used in the formulation are stated to be well-known and used in currently authorised parenteral and non-parenteral preparations licensed for paediatric use.

### 2.3.2. Pharmacology

***Primary pharmacodynamic studies***

Glycopyrronium bromide is a synthetic, nonselective antagonist of peripheral muscarinic cholinergic receptors, and therefore has indirect effects on a variety of tissues and organs that are innervated by postganglionic cholinergic nerves, as well as smooth muscle that respond to acetylcholine.

These effects include actions on the cardiovascular system, respiratory tract, gastrointestinal (GI) tract, eyes, and glandular tissues, among others. Cholinergic stimulation (i.e., increased “vagal tone”) of cardiac tissue typically results in a decrease in cardiac rate (a negative chronotropic effect), a decrease in the rate of conduction within the sinoatrial and atrioventricular nodes (a negative dromotropic effect), and a decrease in the force of contraction (a negative inotropic effect).

According to the cited non-clinical studies on non-clinical pharmacodynamics, the affinity of glycopyrronium bromide to muscarinic acetylcholine receptors M1-M5 seems to be varying. Glycopyrronium was shown to have high affinity for all five muscarinic acetylcholine (ACh) receptor subtypes. Based on studies in transfected Chinese hamster ovary (CHO) cells the affinity of glycopyrronium bromide for human muscarinic receptors was determined to be in the order,  4 (pKi = 10.26) > M1/M3 > M5 > M2 (pKi = 9.67) (Casarosa et al., 2009).

In rats, methacholine-induced lacrimal hyper-secretion was antagonised by orally administered glycopyrronium. Likewise, glycopyrronium bromide reduced gastric secretion and motility in pyloric-ligated (Franko, 1962) and in histamine-stimulated rats with permanent gastric fistulas (Kowalewski, 1970). In anaesthetised dogs, intravenous or oral doses of glycopyrronium markedly reduced intestinal tone and moderately inhibited amplitude of intestinal contractions (Franko, 1062). In a more recent study in dogs, low intramuscular doses of glycopyrronium completely inhibited gastric motility for at least 30 minutes, whereas higher doses caused a cessation of activity for more than 3 hours (Burger, 2006). A reduced volume of methacholine-induced salivary secretion was demonstrated in dogs following an i.v. dose of glycopyrronium (Franko, 1962).

In a study by Posey et al. (1970), glycopyrronium (glycopyrrolate, 2 mg) given orally 4 times daily to dogs, induced ultrastructural parietal cell alterations and profound cytoplasmic vacuolization. The mitochondrial alterations are by the Applicant assumed to be related to drug-induced enzymatic effects. As similar changes were observed with atropine sulphate and propantheline bromide, a general anticholinergic effect may

explain the findings. The Applicant argues that no clinical relevance of this effect is expected, as acid-secreting parietal cells undergo continuous renewal and because treatment of patients with duodenal ulcers with GP for one year did not reduce parietal cell mass (Kaye, 1969). As no clinical concerns regarding this effect have been presented, the conclusion by the Applicant is considered plausible.

***Secondary pharmacodynamic studies***

Secondary pharmacodynamics effects of glycopyrrolate were observed as local anaesthetic properties when injected intradermally to guinea pigs or applied topically to the cornea of rabbits (Franko, 1962).

***Safety pharmacology programme***

Glycopyrronium bromide was not evaluated in the standard battery of safety pharmacology studies. The only non-clinical studies cited are very old (from 1962 and 1978; Franko et al., and Proakis et al., respectively) and both publications give very limited experimental detail, as also pointed out by the Applicant. In one early study, there were no effects on heart rate or carotid arterial pressure in anaesthetised dogs, and no effects on ventilation were reported (Franko, 1962). The penetrance of glycopyrronium bromide across the blood brain barrier was variable, although seemed minimal, in dogs, cats and mice. In dogs, the response in blood pressure to glycopyrronium was also variable between studies.

***Pharmacodynamic drug interactions***

No non-clinical studies were performed or cited regarding pharmacodynamic drug interactions for glycopyrronium bromide this was considered acceptable by the CHMP.

## 2.3.3. Pharmacokinetics

No new pharmacokinetic studies were performed for this application and two publications from 1973 and 1978 were cited. One publication concerns absorption, distribution and metabolism of $^{14}$C-labelled glycopyrrolate in the mouse (Kagiwada, 1973), and the other (Proakis 1978) describes the penetration of glycopyrrolate and atropine across the blood-brain and placental barriers in dogs.

The Applicant has provided brief descriptions of the absorption and distribution of glycopyrronium bromide. Following oral administration of 4.83 µCi/mouse, small amounts of radioactivity were present in the blood by 0.5 hours and remained detectable for up to 6 hours at concentrations of 1.1-1.6 µµCi/mg. Absorption was poor due to the highly ionised and water soluble nature of the drug; 1.9% of the dose was found in the stomach and 6.4% in the small intestine at 3 h post-dose (Kagiwada, 1973). Following i.v. dosing of 0.966 µCi/mouse, the peak of radioactivity was seen at 5-10 min after administration (Kagiwada, 1973).

Following oral and i.v. administration of radiolabelled glycopyrronium to mice, total radiolabelled components were rapidly distributed throughout the body. High levels of radioactivity were observed in highly perfused tissues (kidney, liver, small intestine and various glands) but not in the brain. Autoradiogram did not reveal any radioactivity in the foetus following administration to pregnant animals (Kagiwada, 1973).

After multiple oral administration of radiolabelled glycopyrronium at 3.86 µCi/mouse/day over 1 week, the radioactivity disappeared entirely from organs at 72 hours after the last dose, and accumulation was not observed (Kagiwada, 1973).

The metabolites of glycopyrronium, 1,1-dimethyl-3-hydroxypyrrolidinium bromide α-(2- or 3-hydroxycyclopentyl) mandelate ($M_1$), 1, 1-dimethyl-3-hydroxypyrrolidinium bromide benzoyl formate (M2) and 1,1-dimethyl-3-hydroxypyrrolidinium bromide (M5), were detected mainly in the liver and kidney

(Kagiwada, 1973). After oral dosing, M2 was the most prevalent metabolite in urine, followed by M1, and glycopyrronium was not detected. Similar concentrations of M1 and M2 were found in the liver and kidney. Entero-hepatic circulation is presumed to account for these findings.

Excretion of an orally administered dose was about 7.6% in urine, about 78.9% in faeces and no drug was detected in expired air (Kagiwada, 1973).

Regarding the paper by Proakis, 1978, the Applicant states in the Pharmacokinetics Written Summary that: '*This study shows that glycopyrronium is a selective peripheral anticholinergic agent and thus resistant to penetration across the BB and placental barriers.*' However, this could be misinterpreted to indicate that glycopyrronium bromide does not at all penetrate the blood-brain barrier, which is not considered to be in accordance with the contents and results described in the article. Taking into account that Sialanar is indicated for chronic use in the paediatric population, and as it is known that contagious disease may enhance the passage across lipid membranes such as the blood-brain barrier, the Applicant was asked to address possible safety issues (e.g. neurodevelopmental consequences or toxicity) related to the ability of glycopyrronium bromide to cross the blood-brain barrier, even if in minimal amounts in the proposed population. According to the Applicant, CNS effects occur at a low rate and will be included in any clinical decision on dose adjustments. The Applicant therefore considers that in view of the clinical experience at hand no additional nonclinical investigation of such effects is warranted.

The use of only two (old) publications seems to greatly limit the translation of non-clinical data into the clinical use of glycopyrronium bromide. However, the pharmacokinetics of GP have been thoroughly discussed in clinical sections and the need for additional nonclinical studies on this subject, is not considered necessary.

## 2.3.4. Toxicology

No new toxicology studies were performed in support of the Sialanar application. According to the Applicant, only very few published articles are available on the toxicology of glycopyrronium, and these date from 1962, 1970 and 1998.

**Table 1 Summary of presented toxicology studies and publications.**

| Study type | Route of administration/time | Species | Dose administered | References |
|---|---|---|---|---|
| Single dose toxicity | i.v., i.p., p.o./single dose | Mouse, rat, rabbit, dog, cat | n.s. | Franko, 1962<br>Dollery, 1998 |
| Repeat dose toxicity | p.o. | Dog | 4, 16 or 64 mg/kg | Dollery, 1998 |
| Local tolerance | Topical to skin/single | Rabbit (female) | 0.1, 0.5, 1, 5 or 25 mg/ml | Franko, 1970 |
| Reproductive toxicity | p.o in diet /3-5 wk | Rat | 0, 32.5, 63, 130 mg/kg | Franko, 1970 |

i.v.= intravenous; i.p. = intraperitoneal; p.o. = oral; n.s.= not stated

***Single dose toxicity***

Sparse data are reported in the literature for glycopyrronium bromide following single oral, intraperitoneal (i.p.) or intravenous (i.v.) administration to mice, rats, rabbits, cats and dogs.

**Table 2 Franko, 1962, 1970**

| Species | Sex | Route | $LD_{50}$ (mg/kg) | 95% CL |
|---|---|---|---|---|
| Mouse | M | i.v. | 14.7 | 11.9-18.4 |
| | M | i.p. | 112 | 93-134 |
| | M | oral | 550 | 430-704 |
| | F | i.p. | 107 | 100-115 |
| Rat | F | i.v. | 14.6 | 13.9-15.3 |
| | F | oral | 1280 | 1180-1389 |
| | M | oral | 1150 | 915-1440 |
| | F | i.p. | 196 | 177-217 |
| Rabbit | Either | i.v. | 25* | |
| Dog | Either | i.v. | 15-30* | |
| Cat | Either | i.v. | 15-30* | |

CL = confidence limit
*approximate values
Data source: Franko,1962; Franko,1970; Dollery, 1998

Signs of acute toxicity were found to be similar in all species (mouse, rat, rabbit, dog and cat) regardless the route of dosing. These included mydriasis (all species), tremors, decreased motor activity, clonic and tonic convulsions, respiration failure and death. In rats and mice, absorption of a lethal quantity was not readily accomplished via the oral route. The LD50 values for all species after i.v. dosing was found to be in the range 15-30 mg/kg.

***Repeat dose toxicity***

The Applicant only refers to one chronic, oral repeat dose toxicity study in dogs (Dollery, 1998). The applicant summarizes that in repeated dose toxicity studies in mice, rats, and dogs with oral drug administration or drug administration by inhalation, an exaggerated pharmacodynamic activity of glycopyrronium was observed at high dose levels but no other toxic effects were reported. No risk of adverse effects is expected at the intended therapeutic dose levels in patients.

***Genotoxicity***

No genotoxicity studies were performed and according to the Applicant, no data are available in the public domain. Please refer to non-clinical discussion.

***Carcinogenicity***

No carcinogenicity studies were performed. According to the Applicant, no data are available in the public domain. Please refer to non-clinical discussion. The lack of carcinogenicity data is of concern as it does not allow to sufficiently characterize the safety profile.

***Reproduction Toxicity***

Only one published study from 1970 (Franko) was cited in the section Reproductive and Developmental Toxicity.

Groups of 20 male and 20 female rats were divided into groups of 5 and given glycopyrronium in the diet at doses of 0, 32.5, 63 or 130 ppm for 3-5 weeks. They were then mated. An additional mating used control females that had borne 3 normal litters and treated males that had sired no litters in previous matings; the males were on control diet for 3 weeks prior to the mating. Litters were examined for abnormalities, although it is not stated what these examinations included and there are no data for skeletal or visceral abnormalities.

A summary of reproductive performance in rats given glycopyrronium shows a decrease in the rate of conception and in survival rate at weaning (Table below). Examination of offspring revealed no abnormalities attributable to drug administration.

**Table 3 Summary of reproductive performance of rats given glycopyrronium**

| Parameter | Control | | | Glycopyrronium | | |
|---|---|---|---|---|---|---|
| | First litters | Second litters | Third litters | First litters | Second litters | Third litters |
| No. litters/group | 19/20 | 18/20 | 18/20 | 14/20 | 13/18 | 13/18 |
| No. stillbirths | 1 | 0 | 7 | 8 | 1 | 9 |
| Mean no. live young at birth | 11.2 | 10.7 | 12.1 | 7.7 | 8.8 | 8.0 |
| Lactation index* | 93 | 93 | 92 | 68 | 69 | 96 |
| Mean weight (g) | | | | | | |
| Birth | 6.0 | 6.2 | 6.0 | 6.1 | 6.0 | 6.2 |
| weaning | 33.6 | 37.6 | 41.3 | 34.0 | 34.8 | 41.3 |

* No. pups weaned / no. pups alive at birth x 100

***Toxicokinetic data***

No toxicokinetic data was submitted. Please refer to non-clinical discussion. The lack of toxicokinetic data is of concern as it does not allow to sufficiently characterize the safety profile.

***Local Tolerance***

Glycopyrronium bromide is intended for oral application. There are no tolerance studies on the mucosa but glycopyrronium applied topically to the skin of female rabbits at doses of 0.1, 0.5, 1, 5 or 25 mg/ml saline, 0.2 or 2 mg/ml water, or 200, 632 or 2000 ppm in water produced slight erythema of about 24 h duration with the lowest dose, and higher doses caused slight oedema and more persistent erythema (Franko, 1970). Only minimal signs of toxicity even though systemic absorption occurred as indicated by eye changes (Franko, 1970). As in a paediatric clinical trial (Zeller, 2012) no reports of mucosal irritation were reported these findings were considered without clinical relevance.

***Other toxicity studies***

No non-clinical literature describing the toxicity of glycopyrronium bromide in juvenile animals was presented. Possible toxic effects related to chronic oral administration of glycopyrronium on developing organs, such as

the CNS, neuroendocrine-, immune- and reproductive systems were addressed by the Applicant with reference to clinical data. Insufficient data in the public domain makes it difficult to adequately assess effects on the reproductive system in young adults.

The excipients in the proposed formulation are stated to be well-known and used currently in authorised paediatric oral formulations. The raspberry flavour 1 mg/ml contains 97% of propylene glycol. The WHO has set a maximum permissible daily intake of propylene glycol as a food additive to 25 mg/ kg/day. Nevertheless, clinical data showed that in children from the age of 5 years and adult patients, up to 500 mg/kg/day of propylene glycol could generally be considered safe. In the absence of compelling data this safety threshold was decreased to 50 mg/kg/day in children less than 5 years old as indicated in in CHMP assessment on propylene glycol (EMA/175205/2014). The exposure in this product is equivalent to 0.865 mg/kg/day as defined by the applicant; this is well below the set limits.

## 2.3.5. Ecotoxicity / environmental risk assessment

According to the ERA report provided by the applicant, the projected use of Sialanar would result in maximum predicted environmental concentrations in receiving waters three orders of magnitude lower than the 0.01 µg.L-1 action level. The PECsw value, using the Fpen value of 0.101% is conservatively calculated to be 0.00364 µg.L-1 based on a prevalence of chronic pathological drooling of 0.6% in the sub-population of 3-18 year olds (~16.8% of total European population), and therefore is several orders of magnitude below any predicted no-effect values (derived from QSAR values).

**Table 4 Summary of main study results**

| **Substance (INN / Invented Name): Glycopyrronium bromide (Sialanar)** | | | |
|---|---|---|---|
| **CAS-number (if available): 596-51-0** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 or … | 0.993 (not final; see below) | Potential PBT (N) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 0.993 (not final; see below) | Not B |
| | BCF | N/A | |
| Persistence | DT50 or ready biodegradability | N/A | |
| Toxicity | NOEC or CMR | N/A | |
| **PBT-statement :** | As of now (06 April 2016), no final conclusion can be drawn. The report from the experimentally derived LogKow still awaits from the company. | | |

| ***Phase I*** | | | |
|---|---|---|---|
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| $PEC_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.00364 | µg/L | < 0.01 threshold |
| Other concerns (e.g. chemical class) | | | |
| ***Phase II Physical-chemical properties and fate*** | | | |
| **Study type** | **Test protocol** | **Results** | **Remarks** |
| Adsorption-Desorption | OECD 106 or … | $K_{oc}$ = N/A | Not performed |
| Ready Biodegradability Test | OECD 301 | N/A | Not performed |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50, water}$ = N/A<br>$DT_{50, sediment}$ = N/A<br>$DT_{50, whole\ system}$ =N/A<br>% shifting to sediment = N/A | Not performed |

The CHMP recommends the following points for further investigation:

According to the *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/44609/2010 Rev. 1), '*Log $K_{ow}$ should be determined experimentally. A calculated Log $K_{ow}$ value is generally not acceptable'* and *'QSARs and read-across cannot replace the studies asked for in the guideline on the ERA of medicinal products for human use.* The Applicant may perform a study to determine LogKow experimentally after marketing authorisation and to submit the results.

If indeed the LogKow remains below 4.5 in the future experimental study no further assessment of potential environmental risk is required for this proposed prescribed use of glycopyrronium bromide. If logKow >4.5, further risk assessment will be necessary and may be performed.

## 2.3.6. Discussion on non-clinical aspects

The Applicant has presented a non-clinical dossier for glycopyrronium bromide, which is based on bibliographical data, in line with the requirements under Article 10a of Directive 2001/83/EC. The non-clinical references comprise 17 references, in addition to several clinical publications. The multitude of non-clinical publications date back from the 1960s and 1970s.

The pharmacodynamic properties of glycopyrronium bromide are generally well-known. The cited articles summarize the muscarinic receptors found in salivary glands, pharmacodynamic effects of glycopyrronium bromide as a nonselective antagonist of peripheral muscarinic cholinergic receptors as well as specific pharmaco-chemistry properties involving quaternary ammonium structure.

Provided references were focused on gastrointestinal tract and central nervous system effects and no sufficient references were provided to support the salivary inhibition effect after oral administration. However, pharmacodynamic effects of glycopyrronium bromide as a nonselective antagonist of peripheral muscarinic cholinergic receptors as well as specific pharmaco-chemistry properties involving quaternary ammonium structure are well known and deemed as sufficient to support the proof of concept of the intended indication.

The safety pharmacology studies cited are old (1960s), give little experimental detail, and are not considered to be in line with current guidelines and GLP.

The known cardiovascular safety issues of glycopyrronium bromide in the clinical setting may explain the lack of new non-clinical safety pharmacology studies of cardiovascular effects. Cardiovascular safety is addressed in appropriate sections of the clinical safety assessment.

The described pharmacokinetic properties of glycopyrronium bromide in non-clinical species is very limited but the lack of new pharmacokinetic studies for this application is considered acceptable as clinical data supersede non-clinical data.

The penetrance of glycopyrronium bromide across the blood brain barrier was variable, although seemed minimal, in dogs, cats and mice. In dogs, the response in blood pressure to glycopyrronium was also variable between studies. As a consequence of its quaternary charge glycopyrronium has limited ability to penetrate the blood brain barrier. The potential safety concerns regarding passage of GP over the blood-brain barrier in children with neurological disorders, is of concern as in the Mier, 2000 article, 23% treated with GP vs. 3% treated with placebo had behavioural changes this is further addressed in the safety sections and clinical concerns on neurodevelopment remain.

The only publication on repeat-dose toxicity (Dollery, 1998) presents only subtle experimental detail and does not meet the regulatory expectations of at least 6-month data (oral administration) in a rodent and 9-month data in a non-rodent species and is not considered sufficient for bridging to the chronic dosing regimen of glycopyrronium bromide in children proposed for this application. 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 bromide. In the absence of robust bibliographic data to the chronic oral dosing in the paediatric population is not supported.

The Applicant refers to non-clinical genotoxicity or carcinogenicity studies from public assessment reports. The applicant summarizes that the genotoxicity studies did not reveal any mutagenic or clastogenic potential for glycopyrronium bromide and the carcinogenicity studies in transgenic mice using oral administration and in rats using inhalation administration revealed no evidence of carcinogenicity. However, reference to public assessment reports do not fulfil the requirements of annex I of Directive 20001/83/EC and do not substitute the need to provide data. Clinical Safety data from published controlled trials or other publications are insufficient. Adequate justification for the lack of such data has not been presented. In addition, the dossier lacks a proper justification for the missing toxicokinetic data to allow extrapolation of safety margins in the intended population, including children > 3 years.

Only one study from 1970 (Franko, 1970) was cited in the section Reproductive and Developmental Toxicity. No experimental detail is available. It is stated, however, that glycopyrronium was administered in the diet. As no blood samples appear to have been drawn, the actual exposure of the animals to glycopyrronium may have been limited. Taking into account the significant food interaction seen with glycopyrronium in the clinical setting, the actual bioavailability and exposure of the animals to glycopyrronium in this study is questionable.

The Applicant considers that clinical use of glycopyrronium in children negates the need for further non-clinical data regarding repeat-use toxicology, reproductive/developmental toxicology, genotoxicity and carcinogenicity data. This view is not supported. Published and assessable data of sufficient quality regarding genotoxicity, carcinogenesis and reproductive and developmental toxicity are still considered necessary in order to complete the non-clinical part of this submission. In view of the chronic use of this substance and the characteristics of the target population, these data cannot be substituted by clinical safety results gained with glycopyrronium bromide during short-term use, in other indications or in adults.

### 2.3.7. Conclusion on the non-clinical aspects

Without robust clinical safety data, the lack of published data regarding repeat-dose toxicology, reproductive/developmental toxicology, genotoxicity and carcinogenicity data does not allow to address uncertainties related to the safety profile of this substance. Extrapolation of safety margins to the proposed target population are not considered adequate due to lack of toxicokinetic exposure data.

Based on the provided non-clinical dossier, the application for glycopyrronium bromide for treatment of sialorrhoea in children aged 3-18 years, is considered non-approvable at the present based on the submitted data.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

According to Article 10a of Directive 2001/83/EC, if the Applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the EU for at least 10 years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I of the abovementioned Directive, it is possible to replace results of pre-clinical and clinical trials by detailed references to appropriate scientific literature.

In support of this PUMA application, the Applicant relies in particular on three published Phase III clinical trials, Zeller, 2012a, Zeller, 2012b and one with crushed and gelatin encapsulated tablets to allow for placebo comparison (Mier, 2000) which are claimed to demonstrate the clinical efficacy and safety of GP for the treatment of sialorrhoea in the paediatric population with neurological disorders. The medicinal product used in Zeller studies is a GBOS presentation of lower concentration (1 mg/5 mL or 0.2 mg/mL) than the Applicant's presentation (0.4 mg/mL), and was approved for the indication 'reduce chronic severe drooling in patients aged 3-16 years with neurological conditions associated with problem drooling (e.g. cerebral palsy)' by the Food and Drug Administration (FDA) in the US in 2010 (Cuvposa PI, 2013).

In total clinical data are available from five completed studies in the paediatric population that inform the efficacy profile of GP when used for the proposed indication:

a) Two pivotal studies in the paediatric population (Zeller, 2012a; Mier, 2000);

b) Three supportive studies in the paediatric population (Zeller, 2012b; Blasco, 1996; Stern, 1997)

A further supportive study (Arbouw, 2010) was submitted which examined the efficacy of GP for the treatment of sialorrhoea in adults with Parkinson's disease (PD).

Furthermore the data on an open label, single dose, two way crossover study to compare the bioavailability of 2 mg glycopyrronium bromide from Sialanar (2 mg/5 ml) (test product) with that of 2 mg glycopyrronium

bromide from the product used in Zeller studies (1 mg/5 ml solution) in healthy adults (study PRO/GLY/001) were submitted in order to bridge to Zeller studies.

Hence, apart from the PK/PD information retrieved from study PRO/GLY/001 for the purpose of bridging to the data in the literature, the clinical pharmacology data were derived from the literature.

***GCP***

This MAA contains two main clinical studies (Zeller 2012a and Mier 2000) submitted as published literature. The Zeller 2012a study was reportedly conducted in accordance with GCP. There is no statement about GCP compliance for the latter study. There are no statements about any GCP inspection.

**Table 5 Tabular overview of clinical studies**

| Study ID | No. of study centres / locations | Design | Study Posology | Study Objective | Subjs by arm entered / compl. | Duration | Gender M/F; Median Age | Diagnosis Incl. criteria | Primary Endpoint |
|---|---|---|---|---|---|---|---|---|---|
| Zeller, 2012a | 10 / USA | Rand., DB(?), PC, PG | OS TID (1mg/5mL) | Efficacy/Safety | TD 20, PC 18/ 18, 16 | 8w | 22/14; TD 10.2y, PC 8.7y | Drooling due to CP (Ch+Ad) | mTDS responder rate (≥3p) |
| Zeller, 2012b | 28 / USA | OL, SG | OS TID (1mg/5mL) | Safety/Efficacy | 137/103 | 24w | 77/60;11.0 | Drooling due to CP (Ch+Ad) | As above |
| Mier, 2000 | 2 / USA | Rand., DB, PC, PG | Capsules (0.6 mg), TID | Efficacy/dose-ranging | 39/27 | 1 8w (1w BL, 8w TD/PC, 1w WO, 8w PC/TD) | NR;NR | Drooling due to CP (Ch+Ad) | mTDS mean change? |
| Stern, 1997 | 1? / Australia | OL, SG | Formulation not stated, OD | Efficacy (descriptive) | 24/22 | 5w-28m (flexible?) | NR;NR | Drooling due to CP (Ch-yAd) | Scale by Thomas-Stonell |
| Blasco, 1996 | 1 / USA | OL, SG | Formulation not stated, 1-5 times/d | Efficacy (descriptive) | 40/38 | 8m-4y (flexible) | NR;12.5y | Drooling due to CP (Ch-yAd) | Drooling worse, better or the same |
| Arbouw, 2010 | 1 / NL | Rand., DB, PC, CO | OS TID (0.2 mg/mL) | Efficacy/Safety | 23/23 | 4w (1w each BL, TD/PC, WO, PC/TD) | 19/4;70.0 | Drooling due to PD (adults) | mTDS responder rate (=scoring improved with ≥30%) |

## 2.4.2. Pharmacokinetics

Pharmacokinetic information on GP was based on data from literature and one bioequivalence/bioavailability study comparing GBOS (the formulation for the applied product) and the formulation used in Zeller studies.

**Literature studies**

**Table 6 Pharmacokinetics in children**

| | Objective | Design | Subjects | Number of subjects | Treatment |
|---|---|---|---|---|---|
| Rautakorpi, 1994 | PK of GP in children | Open label, parallel group | Children undergoing minor surgery | N=26, 3 age groups | i.v. 5 µg/kg |
| Rautakorpi, 1998 | Bioavailability of oral GP | Open label, cross over, oral, then i.v. | Children undergoing minor surgery | N=6 | Oral 50 µg/kg<br>i.v. 5 µg/kg |
| Rautakorpi, 1996 | Determine CNS bioavailability | Open label | Children with hydrocephalus | N=12 | i.v. 5 µg/kg |

**Table 7 Pharmacokinetics in adults**

| | Objective | Design | Subjects | Number of subjects | Treatment |
|---|---|---|---|---|---|
| Ali-Melkkilä, 1989 | PK/PD of GP after oral, i.v. and i.m. adm | Parallel group, single dose | HV undergoing ocular surgery | N=18 | Oral 4 mg<br>i.m. 8 µg/kg<br>i.v. 6 µg/kg |
| Ali-Melkkilä, 1990a | CSF BA of GP<br>PD of GP | Single-dose | Patients undergoing vaginal hysterectomy | N=9 | i.m. 8 µg/kg |
| Ali-Melkkilä, 1990b | PK of GP | Single-dose | Patients undergoing caesarean section | N=8 | i.m. 8 µg/kg |
| Kaltiala, 1974 | PK of radiolabelled GP | Single-dose | Patients undergoing gallstone removal | N=6 | i.v. 3,65 µCi |
| Kirvelä, 1993 | PK of GP in uraemic pts | Single-dose | 11 uraemic patients undergoing renal tx and 7 patients ASA1 undergoing | N=18 | i.v. 4 µg/kg |

| | | | | | |
|---|---|---|---|---|---|
| | | | general surgery | | |

The information on the PK of GP in children was derived from studies reported in literature, all single dose studies with either i.v. or oral administration of GP in patients undergoing surgery. In adults, the literature studies (all single dose, i.v., i.m. or oral administration) were supplemented by the bioequivalence/bioavailability single dose study (PRO/GLY/001) in healthy volunteers, where GBOS (test product) and the product used in the Zeller studies (hereinafter 'reference product') were compared in terms of $C_{max}$ and $AUC_{0-t}$.

The oral bioavailability of GP is very low and variable. The oral bioavailability in children was estimated at 3.3% following a single dose of 50 µg/kg (range 1.3-13.3, Rautakorpi 1998). Based on data from the Robinul prescribing information, the Applicant suggests a BA of GBOS of 5.8%, which is less than the BA reported in the literature of 10-25% of GP.

***Absorption***

The bioavailability of the GBOS formulation compared to the reference product formulation was investigated in a bioequivalence study. Conventional 80-125% criteria for bioequivalence were employed. Bioequivalence could not be demonstrated as the confidence interval for the ratio (test vs. reference) for both Cmax and AUC0-t exceeded 1. A 25% higher exposure and a 22% higher Cmax with GBOS were observed. Furthermore, PK variability was large when considering the rather narrow therapeutic interval of GP.

No food interaction studies were conducted with GBOS, and the BE/BA study PRO/GLY/001 was performed in fasting subjects. The Applicant did not refer to any literature in order to address the influence of food on the bioavailability of GBOS. In the product information for the reference product, the drug is recommended to be taken before or after meals, as food reduces the absorption of the drug.

***Distribution***

The volume of distribution (Vd) was evaluated in children and adults in two studies (Rautakorpi, 1998 and Ali-Melkkilä, 1989), and corresponds that of total body water. The Vd was higher in children (1.3-1.8 L/kg) compared with 0.64 L/kg in adults, corresponding well the larger total body water volumen in children. Distribution to the CNS was shown in 4/9 children with hydrocephalus, undergoing shunt operations, with the highest concentration in two patients with a shunt infection however no GP in CSF in adult patients undergoing vaginal hysterectomy was found.

***Elimination***

The predominant route of elimination of glycopyrronium bromide (GP) is by renal excretion; approximately 65% of an i.v. dose is renally excreted within the first 8-24 hours (Kirvelä, 1993 [m2.7.2, Table 20]; Ali-Melkkilä, 1990a; Ali-Melkkilä, 1990b, and approximately 85% after 48 hours (Kaltiala, 1974). A much smaller proportion (~5%) is eliminated in the bile (Kaltiala, 1974).

Two studies in children reported clearance following an i.v. dose of 5 µg/kg in children 0-14 years of age. In children aged < 1 year and 1-3 years, respectively, clearance ranged from 1.01 L/h/kg to 1.41 L/h/kg. In children aged 7-14 years, clearance was estimated to 1.09 L/h/kg. Elimination half-life varied from 46.7 min to 139 min. No half-life values following oral administration in children were reported.

**Table 8 PK parameters following single dose i.v. GP (5 µg/kg) in children 7-14 years of age**

| $AUC_{0-\infty}$ (µg.min/L) | $t_{½,z}$ (min) | $V_{ss}$ (L/kg) | Cl (L/h/kg) |
|---|---|---|---|
| 276.3 (210.2 – 502.8) | 139 (73 – 239) | 1.37 (0.75 – 2.64) | 1.09 (0.60 – 1.43) |

Data source: Rautakorpi, 1998

Key: AUC = area under curve; Cl = clearance; $t_{½,z}$ = elimination half-life; Vss = distribution volume at steady state

Note: Data are medians (ranges)

In adults, the elimination half-life has been shown to be dependent of the route of administration (Ali-Melkkilä, 1989), with the shortest half-life following i.v. administration of 0.83 ± 0.27 hrs (~50 min). Elimination half-life following i.m. administration was 75 minutes and following oral administration 2.5-3 hours, with highly variable results.

Studies have found that 50-80% of GP is excreted as unchanged drug, in the urine (primarily) and bile (Kaltiala, 1974; Ali Melkkilä, 1990a). The renal elimination of GP involves both glomerular filtration and proximal tubular secretion. Most of GP is eliminated unchanged, and it appears that only a small part of GP is metabolised.

***Dose proportionality and time dependencies***

No formal evaluations of the dose proportionality and time dependency of the PK were performed as only single dose studies with one dose level only were done. This pertains to both children and adults. An indirect comparison of the Cmax in two studies, Ali Melkkilä, 1989 and PRO/GLY/001 was provided, showing a doubling of the Cmax value in adult patients treated with 2 and 4 mg: 0.332 µg/ml and 0.76 ± 0.35 µg/L.

In children, the inter-individual variability of Cmax (median 0.37 µg/L, ranges 0.19-0.44) after oral administration of 50 µg/kg appeared to be less than both AUC0-t (median 106.6 µg.min/L, ranges 38.5-278.7), and Tmax (median 90, ranges 30-480). Also, in comparison with the adults, less variability in Cmax is suggested. No data on intra-individual variability was presented for children.

In adults, following stage 1 of study PRO/GLY/001, the intra-individual variability of GBOS was estimated in order to calculate the sample size for stage 2. Stage 1 showed an intra-individual variability of 37.5% for Cmax and 31.1% for AUC0-t. A quite large inter-individual CV% was seen as regards Cmax and AUC0-t, largest for the reference product, where the Cmax CV% was 95%, and the AUC0-t CV% was 82%. The corresponding CV% for GBOS were smaller with 62% for both Cmax and AUC0-t.

***Special populations***

For special populations, only single dose studies were submitted for the presentation of GP PK, hence no information as regards the steady state PK in special populations is provided. This means that the PK in children, adults and renal disease patients has been evaluated after single doses of GP only. PK effects of the covariates weight, race, and gender were not characterised.

The PK across age ranges of 0.2-14 years, after i.v. administration of 5 µg/kg, did differ for the children aged 1.3 years. However, the PK parameters were highly variable, and it is suggested that the PK parameters are comparable for all ages.

The PK of GP was evaluated in 11 uraemic patients undergoing renal transplantation with a mean serum creatinine concentration of 731 ± 267 µmol/L (SD), compared with 7 patients without renal impairment (s-crea 75 ± 17 µmol/L), ASA1, undergoing general surgery, (Kirvelä *et al*, 1993). The elimination was significantly prolonged in the renally impaired patients, with twice the elimination half-life, a three times higher AUC, and a three times lower clearance, as compared to subjects with normal creatinine.

In summary the impact of renal impairment was significant after single doses, with increased exposure and prolonged half-life, and it is expected that with multiple dosing, similar effects will be seen.

Given the minor importance of hepatic metabolism in the elimination of glycopyrronium, it is agreed that a study in patients with hepatic impairment is not warranted since the impact of reduced metabolising capacity is likely minimal.

***Pharmacokinetic interaction studies***

No dedicated drug-drug interaction studies were performed by the Applicant. It is stated by the Applicant that in study PRO/GLY/001, no drug/drug interactions were observed during the study. Concomitant medication was oral contraceptives in 11/27 female study participants, other medications were acetaminophen and ophthalmic preparations taken 12 hours post dose. Hence, the drugs taken are not supposed to interfere with PK assessment. The Applicant has conducted a review of pharmacokinetic and pharmacodynamic interactions relevant for glycopyrronium or for anticholinergic medicines in general based on the website Drugs.com and additional publications where relevant. The site contains a library of reference information which includes content from Cerner Multum, Micromedex from Truven Health Analytics, Wolters Kluwer Health, U.S. Food and Drug Administration (FDA), Physicians' Desk Reference, A.D.A.M., Stedmans, AHFS, Harvard Health Publications, North American Compendiums, PharmaLive, & Healthday. Drugs.com is certified by the TRUSTe online privacy certification program and the HONcode, Health on the Net Foundation (see also safety assessment).

Most of the listed interactions are not specific to glyopyrronium, but apply to anticholinergic medicines in general. The information has been extracted from a number of well-recognized sources and conclusions in terms of recommendations (contraindications, cautions as well as more specific recommendations in the SmPC) for each medicine/class of medicines is generally supported.

***Pharmacokinetics using human biomaterials***

No pharmacokinetic studies using human biomaterials were submitted. This was considered acceptable by the CHMP.

## 2.4.3. Pharmacodynamics

***Mechanism of action***

Anti-muscarinic drugs are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves, as well as being inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation. GP inhibits the pharmacological action of acetylcholine, hence, an anti-cholinergic effect is achieved. The effect of GP in drooling is judged by the clinical response, and no biomarkers are available. The antisialogoque effect was only assessed in adults, heart rate in both children and adults.

The mechanism of action of GP is well-known, and the anti-cholinergic effect, hyposalivation, is the desired effect for the sought indication drooling. Hence, the scientific rationale is understood and accepted.

***Primary and Secondary pharmacology***

*Effect of GP on heart rate*

Vagolytic effects has been shown to occur at a plasma GP concentration of 10 µg/L. Only one study reported Cmax of more than 10 µg/L: In adults undergoing vaginal hysterectomy a Cmax of 15.79 µg/L was seen following 8 µg/kg i.m. Heart rate increased within ½ hour by app. 20 beats/min, which resolved in 1-3 hours. No other submitted studies reported Cmax values above 10 µg/L following oral administration.

In the studies by Rautakorpi in children, no effect on the heart rate or blood pressure after an i.v. dose of 5 µg/kg or an oral dose of 50 µg/kg was observed in children aged ½-14 years undergoing minor surgery.

In the studies by Mirakhur in children, the PD of GP administered i.v. or i.m. at different dose-levels for the prevention of the oculo-cardiac reflex effect during squint surgery or elective ophthalmic surgery was evaluated. Oculo-cardiac reflex was defined as a decrease in heart rate of ≥ 20%, or the occurrence of arrhythmia during traction of the eye muscles, irrespective of baseline heart rate. No oral administration of GP was assessed in these studies. A significant increase in heart rate from baseline was observed following i.m. administration in children undergoing elective ophthalmic surgery. Even though the absolute increase in heart rate from baseline was higher for the 7.5 µg/kg dose compared with the 5 µg/kg dose (3-7 heart beats), large SDs preclude any conclusions on a dose-response relationship. The ocular-cardiac reflex (decrease in heart rate of ≥ 20%) was inhibited in GP treated patients undergoing squint surgery to a larger extent as compared with those receiving placebo.

In the study by Mirakur *et al*, 1982c dysrhythmias were infrequent in conscious patients at either (5 or 7.5 µg/kg) dose of i.v. GP (5-10% of patients), but were somewhat higher in anaesthetized patients (25%) after 5 µg/kg. Accelerated junctional rhythm was the main dysrhythmia observed. Dysrhythmia was considerably less frequent in patients who received 7.5 µg/kg GP i.v. compared with patients who received placebo.

Parenteral administration of GP resulted in heart rate increases, but whether these increases are clinically relevant from a safety perspective has not been discussed, only is it stated by the Applicant that no significant increases in heart rate were observed after i.v. and oral administration, respectively.

In adults, the effect of GP on heart rate was assessed in the literature only, showing that following oral administration, at three different dose levels (2, 4, and 8 mg) in healthy volunteers, no heart rate increases were observed, hence no dose-response relationship were noticed (Mirakhur, 1978a). Following parenteral administration, in patients undergoing minor surgery/ECT (Mirakhur, 1979a), significant increases in heart rate were observed, with increasing doses. Heart rate was measured by either palpation or ECG. The heart rate increases usually resolved within 1-3 hours.

*Anti-sialogogue effects of GP*

Ali-Melkkilä, 1989, showed that following an oral dose of 4 mg, just prior to induction of anaesthesia, a significant anti-sialogogue effect was significant after 6 hours only, i.e. a very slow-onset of the PD effect, in these 6 patients undergoing ocular surgery. The effect was followed until 8 hours post-administration.

In a study by and Mirakhur, 1978a, 6 healthy volunteers, received 3 doses of GP, administered either i.v, i.m or orally, i.e. every subject received 9 doses of GP. The results indicated a dose-dependent reduction in salivary secretion, measured by using citric acid placed under the tongue and secretions collected in a jar, although with a slower onset after oral administration. The study ended after 6 hours. The assessment of salivary function was different from study to study. Some used evaluation by a VAS 0-10 scale (mouth

normal – extremely dry), and others had the effect of GP on salivary secretion in patients undergoing surgery evaluated by the anaesthetist, categorizing the mouth as dry, moderately dry or wet. Hence, the methods by which the anti-sialoqoque effect was evaluated differed among the studies submitted.

*Pharmacodynamic interactions*

As stated previously, no dedicated drug-drug interaction studies were performed by the Applicant. However, the Applicant has conducted a thorough review of pharmacokinetic interactions relevant for glycopyrronium or for anticholinergic medicines in general.

## 2.4.4. Discussion on clinical pharmacology

The clinical pharmacology characteristics of Sialanar are based on bibliographical data in line with the requirements under Article 10a of Directive 2001/83/EC. A full study report has been submitted for the bioequivalence/bioavailability study (PRO/GLY/001) comparing the bioavailability of the to-be-marketed GBOS formulation (Sialanar) with the formulation of the product used in the Zeller studies (the reference product), marketed in the US. The study was intended to bridge with the published literature for the pivotal studies.

Study PRO/GLY/001 showed a large difference in the bioavailability of the two products. In the context of an active substance with complex gastrointestinal absorption in particular the excipient sorbitol (known to reduce absorption) in the reference product, may explain the difference in bioavailability between the two formulations.

Due to the higher bioavailability of Sialanar (approximately 20% higher exposure) compared to the reference product the recommended initial dose and dose titration schedule was revised to a 20% lower initial dose and 20% lower dose increments.

After amending the titration schedule bridging to the most recently generated efficacy and safety data on the target population via the target route of administration (Zeller studies) is acceptable. Also all of the GP efficacy and safety data in the target population had been generated using oral formulations (Zeller, 2012 a and b, Mier, 2000, Blasco 1996, Stern 1997, and Bachrach 1998) and can therefore be taken into account. The i.v. and i.m. data has been used to support particular pharmacokinetic, pharmacodynamic and safety discussions related to the drug substance per se and can be considered relevant for this purpose.

Even though during titration efficacy will be balanced against tolerability both products show a high PK variability and pronounced food interaction and the responses may differs from day to day, and even from dose to dose. Also one of the referenced studies by Rautakorpi, 1998, concluded high variability and low bioavailability of glycopyrronium administered i.v. or orally, which is in line with the results of study PRO/GLY/001.

Considering the revised titration schedule and the recommendation to administer Sialanar without food (as is the case of the reference product), the potential detrimental effects of the high pharmacokinetic variability with Sialanar on safety and tolerability (excursions in exposure leading to adverse effects) are considered to be reflected by the by the safety and tolerability data obtained with reference product.

Data from a food interaction study showed that the absorption of a GP product (10 ml, 1 mg/ 5 ml) oral solution is reduced when administered with food. Cmax was 74% lower under fed conditions and $AUC_{0-t}$ was reduced by 78%. No food-drug interaction studies were conducted with Sialanar, and study PRO/GLY/001 was performed in fasting subjects.

To address potential food effects on the bioavailability of Sialanar the applicant justified that the likely direction of the food effect will be the same as for the product used in the Zeller studies, i.e. a marked reduction of exposure – although it may be quantitatively different. The recommendation to dose without food is consistent with the label of the product used in the Zeller studies and likely leads to less PK variability compared to having no recommendations or a recommendation to take with food. It is also considered to reflect best the clinical data obtained with the formulation used in the Zeller studies.

The impact of renal impairment was significant after single doses, with increased exposure and prolonged half-life, and it is expected that with multiple dosing, similar effects will be seen. Based on extrapolation of results from adult subjects with mild to moderate renal impairment, the Applicant proposed a dose reduction of 30% in children with mild or moderate renal impairment. Since Sialanar will be titrated based on an assessment of efficacy and side effects, the proposal was endorsed by the CHMP and included in the SmPC. Given the very limited data, also a warning regarding mild and moderate renal impairment in the SmPC was added. As GP elimination of GP is largely renal and impaired in patients with severe renal impairment, irrespective of the cause the applicant proposed a contraindication for these patients to which the CHMP agreed.

The Applicant provided a thorough review of pharmacokinetic and pharmacodynamic drug-drug interactions relevant for glycopyrronium or for anticholinergic medicines in general. Recommendations on drug-drug interactions (contraindications, cautions as well as more specific recommendations) for each medicine/class of medicines are supported by the CHMP and relevant information has been included into the SmPC.

The Applicant addressed the correlation between GP exposure and adverse events analysing the relative bioavailability study, PRO/GLY/001, for a possible relationship between exposure and frequency of any AE, total number of AEs per subject, frequency of the most common adverse events (headache, dry mouth, and dry throat) and severe adverse events. No firm conclusions can be made on a relationship, although the performed analysis suggested a small trend between the overall exposure and the frequency of AE occurrence and the frequency of dry throat. Further reference was made to the study by Zeller et al, 2012b which reported the relationship between the frequency of AEs and administered glycopyrronium doses. A clear relationship with dose (or dose range) was seen for a number of adverse events.

The presented pharmacodynamic studies confirm the expected effects on heart rate (increase) as well as anti-sialogogue effects of GP. The Applicant has provided a comprehensive overview of the published literature on effects on heart rate induced glycopyrronium (both in adults and in children) as well as limited data from its own relative bioavailability study, PRO/GLY/001.

The applicant presented simulated data suggesting that the plasma concentrations using Sialanar will be somewhere in between what was observed in Rautakorpi, 1998 study using glycopyrrolate orally and intravenously in which no significant increase in heart rate was observed. However this information was considered insufficient by the CHMP.

Only 6 otherwise healthy children in the age 7-14 years were included who underwent surgery, and glycopyrrolate was administered together with anesthesia. It is not mentioned what was used to induce anesthesia, but most likely this could have had an effect on pulse rate. Additionally, the heart rate (median) did increase from approximately 80 at baseline to a maximum of approximately 95 after an intravenous infusion. The same change was not seen after the oral administration but only one oral dose was administered. The plasma concentrations and possible effects on heart rate are expected to be higher at steady state (after approximately 5 doses).

Data from the Rautakorpi 1994 article where 11 otherwise heathy children (aged 3-12 years) who were given an intravenous injection of glycopyrrolate. A mean increase in heart rate similar to the Rautakorpi 1998 article was shown. Again, anesthesia was provided concomitantly. The anesthesia consisted of thiopental, fentanyl, succinylcholine and anesthesia was maintained with 70% nitrous oxide and isoflurane. Most of these medicines will affect blood pressure and/or heart rate.

Therefore articles by Rautakorpi (1994 and 1998) cannot be used to estimate if glycopyrronium has an influence on heart rate and/or blood pressure.

The SmPC gives a warning statement about potential increases in heart rate produced with administration of Glycopyrronium bromide and also the known effect on blood pressure is described however information on heart rate and blood pressure changes in the treatment in children with neurological disorders is insufficient and uncertainty remains with regard to effects on heart rate specifically and to cardiovascular safety in general (see discussion on safety in this assessment report).

### 2.4.5. Conclusions on clinical pharmacology

Considering the revised titration schedule and the recommendation to administer Sialanar without food (as is the case of the reference product) a bridging to the data from the product used in the Zeller studies can be considered acceptable. All of the GP efficacy and safety data in the target population had been generated using oral formulations (Zeller, 2012 a and b, Mier, 2000, Blasco 1996, Stern 1997, and Bachrach 1998) and can therefore also be taken into account in the assessment. The i.v. and i.m. data has been used to support particular pharmacokinetic, pharmacodynamic and safety discussions related to the drug substance per se and can be considered relevant for this purpose.

However, even though during titration efficacy is to be balanced against tolerability in both products (Sialanar and the reference product used in the Zeller studies) both showed a high PK variability and pronounced food interaction and the effects may differ from day to day, and even from dose to dose.

Concerns on potential detrimental effects of the high pharmacokinetic variability with Sialanar remain and it also remains uncertain if the plasma concentrations of Sialanar in children and adolescents with neurological disorder could cause clinically relevant side effects. Information is inadequate on areas of key interest where the pharmacology of glycopyrronium and/or the limited clinical data warrant attention or further investigation: adverse effects on heart rate and blood pressure, pneumonia and urinary retention.

The pharmacological data submitted are considered very sparse and significant uncertainties remain. This is further discussed in the safety chapter of this report.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response study(ies)

No separate dose-response studies were conducted. Instead, dose-response was addressed by using an individualised adaptive titration in fixed steps in studies Zeller, 2012a; Zeller, 2012b; Mier, 2000, but only one of these studies reported efficacy data by dose levels (Mier, 2000; see below).

## 2.5.2. Main studies

### Zeller 2012a. Study title: A double blind, randomized, placebo controlled trial to evaluate the efficacy and safety of oral glycopyrrolate liquid (1 mg per 5 mL) for the management of problem drooling associated with cerebral palsy or other neurologic conditions in children

This was a placebo controlled double-blind trial with eight weeks treatment (two parallel groups). The first four weeks comprised a titration in fixed steps to an individualized optimal dose elevel.

***Methods***

***Study Participants***

Male or female ages 3 to 16 years.

Other inclusion criteria were:

- Weigh at least 12.2 kg
- Have profuse or severe drooling in the absence of treatment so that clothing became damp on most days (approximately 5-7 days per week); and a diagnosis of CP and/or mental retardation or any other neurologic impairment or condition.
- A reliable P/C as determined by the Investigator is living with the subject.

The protocols specifically allowed enrolment of subjects with tracheostomies or gastrostomy feeding tube

Exclusion criteria were:

- Pregnancy
- Use of GP liquid within approximately 24 hours prior to baseline
- Use of any of the prohibited anticholinergic or cholinergic medications specified in the protocol within three plasma half-lives of the medication prior to baseline
- Medical conditions contraindicating anticholinergic therapy including: Glaucoma, obstructive uropathy, uretovesicular reflux, reactive airway disease, myasthenia gravis, hyperthyroidism, cardiac arrhythmias and/or tachycardia, and/or clinically significant ECG abnormalities as determined by the investigator

***Treatments***

1:1 randomization to GP liquid (1 mg/5 mL) or matching placebo. Study medication was administered tid at 7–8 AM, 1–2 PM, and 7–8 PM by the parent/caregiver (or school nurse if the patient is in school during these hours of the day). Baseline measurements of safety and efficacy were made prior to being randomized to either the test product or placebo

Since high fat meals reduce the oral BA of Cuvposa, P/C were advised to administer study drug at least 1 hour before or 2 hours after meals

Doses were titrated over the first four weeks to optimal response, beginning at 0.02 mg/kg tid up to 0.1 mg/kg tid (not to exceed a maximum dose of 3 mg tid, regardless of weight).

After starting at Dose Level 1, doses were increased every 5 to 7 days in increments of 0.02 mg/kg tid, according to a dose titration schedule. If anticholinergic AEs became intolerable, the P/C was instructed to

contact the Investigator, who reduced the dosage to the previous dose-level in the schedule, with the subject continuing to use that dose-level for the remainder of the study (or until AEs require another reduction to the next-lowest dose-level).

If no significant drug-related AEs were reported by the P/C, the investigator increased the subject's dose to the next dosing level. This continued during the 4 week time period, until an optimal individual response or a maximum of 0.1 mg/kg tid or 3 mg tid was attained, whichever was less. During the titration period, investigators assessed subjects every 5 to 7 days by telephone and adjusted the dose until an optimal dose was achieved.

The study assessed P/Cs ability to interpret the signs of efficacy and associated anticholinergic AEs. During the study, each P/C reviewed instructional materials about titrating the dose and observing for AEs in subjects. Caregivers were allowed, through discussion with the child's physician, to adjust dose levels due to concerns about AEs.

***Objectives***

Objectiv of the study was to evaluate the efficacy and safety of GP oral solution (Cuvposa) (1 mg/5 ml) in managing problem drooling associated with cerebral palsy (CP) and other neurological conditions. Problem drooling was defined as drooling in the absence of treatment such that clothing became damp approximately 5 7 days/week.

To assess caregivers ability to identify AEs between visits so that an investigator can optimally titrate the dose.

***Outcomes/endpoints***

The primary efficacy endpoint was responder rate, based on change in degree (severity and frequency) of drooling, as measured by parents/caregivers, using the modified 9-point Teacher's Drooling Scale (mTDS), which was assessed at baseline and at weeks 2, 4, 6, and 8. The mTDS is scored from 1 (dry, never drools) to 9 (profuse: clothing, hands, tray, and objects become wet; frequently). At the request of the FDA, the primary endpoint was changed to "dichotomized mTDS," which defined responders as those having an increase ≥3 units on the mTDS. During each of the scoring days, parents or caregivers (P/C) performed the evaluations. The mTDS score for each evaluation day was calculated by using the mean of the last three daily assessments. The baseline mTDS score for each subject was defined as the last day's mTDS assessment before first dose of study medication. For each subject, the change in score from the baseline score to the score at the last evaluation of the trial was calculated.

Secondary outcomes/endpoints included Global Assessment of Treatment (1 to 5 scale anchored on strongly agree and strongly disagree for the statement "This is a worthwhile treatment" at Week 8 or last visit for withdrawals, and a separate P/C-Reported and Investigator-Reported Global Assessment of Training Manual at Week 8 or last visit for withdrawals asking "The training manual was helpful? Yes or no".

***Sample size***

Thirty-eight subjects were randomised. No statistical justification for the sample size is reported, e.g. the smallest meaningful clinical difference for responder rate between the GOPOS group and the placebo group.

***Randomisation***

Subjects were randomized in a 1:1 ratio to glycopyrrolate or placebo three times per day. Those receiving anti-sialogenic compounds or other medications with anticholinergic or cholinergic activity underwent a washout phase prior to baseline, beginning 8 days before randomization.

***Blinding (masking)***

The test product and placebo were matching (similar in colour and taste).

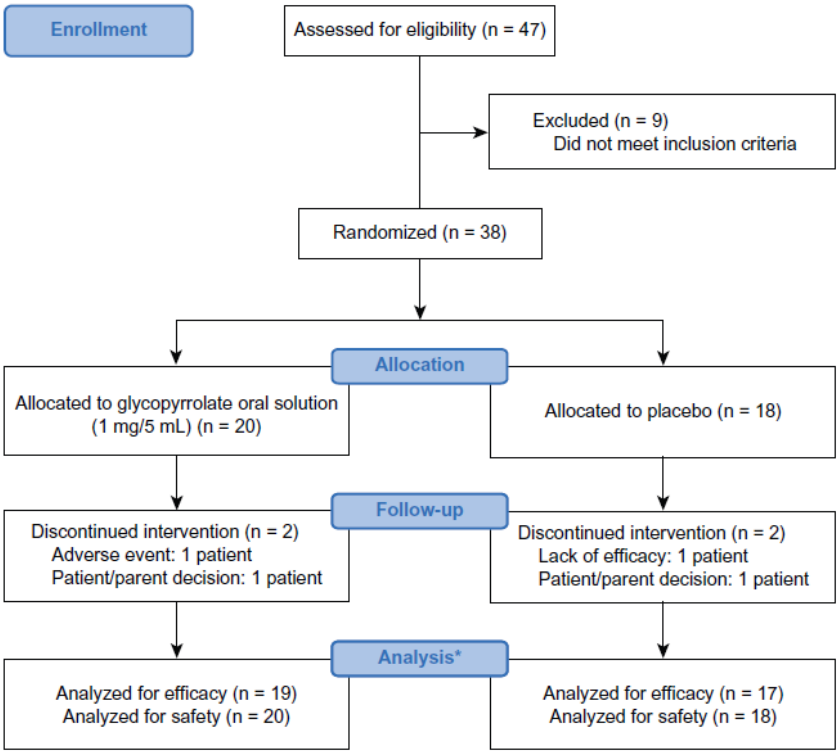
As patients receiving placebo would be expected to continue drooling chronically, caregivers of patients in this group were specifically encouraged to keep patients in the study until at least the end of the 4-week titration period.

***Statistical methods***

Data from all centres were combined. All percentages were based on the total number of patients in each group (two-sided P values). Patients who dropped out before the end of the study had the lowest rank carried forward. All statistical hypothesis tests used a type I (alpha) error of 0.05. All statistical calculations were performed using SAS® software (v 9.1.3; SAS Institute, Cary, NC). According to the statistical analysis plan, all patients who received at least one dose of study drug were to be included in the safety population, and all randomized patients were to be included in the intent-to-treat (ITT) analysis of efficacy. In practice, two patients were randomized to treatment before the protocol was amended to set an upper age limit, and these patients no longer met the inclusion criteria. Thus, efficacy was assessed in a modified ITT (mITT) population, defined as all randomized patients who were within the age range of the final, amended protocol and received at least one dose of study medication. Consequently, these two patients were included in the analyses of safety but not of efficacy.

***Results***

**Participant flow**



**Recruitment**

This study was conducted between November 2002 and April 2007 in the USA. The study duration, from first patient screened to last patient completed, was approximately 4.5 years.

**Conduct of the study**

The study was conducted according to Good Clinical Practice guidelines and in full compliance with the World Assembly Declaration of Helsinki and its most recent amendments. Protocol was amended to set an upper age limit (to 16 years), which led to 1 fewer patient being included in the modified intent-to-treat (mITT) population for the efficacy analysis for both the glycopyrrolate oral solution (1 mg/5 mL) and placebo groups.

A temporary hold was placed on enrolment from November 2005 to September 2006 (10 months) pending receipt of US orphan drug designation for glycopyrrolate liquid, which was granted on June 9, 2006, for the indication "treatment of pathologic (chronic moderate to severe) drooling in paediatric patients" by the US Food and Drug Administration Office of Orphan Products Development.

**Table 9 Baseline data**

| | | Glycopyrrolate oral solution (n=19) | Placebo (n= 17) |
|---|---|---|---|
| Age, years | Mean (SD) | 10.2 (3.8) | 8.7 (4.0) |
| | Range | 4-16 | 3-16 |
| | ≥3 to≤11 | 12 (63.2%) | 12 (70.6%) |
| | ≥12 to≤18 | 7 (36.8%) | 5 (29.4%) |
| Sex | Male | 13 (68.4%) | 9 (52.9%) |
| | Female | 6 (31.6%) | 8 (47.1%) |
| Race | White | 16 (84.2%) | 10 (58.8%) |
| | Black or AA | 2 (10.5%) | 7 (41.2%) |
| | Other | 1 (5.3%) | 0 |
| Ethnicity | Hispanic or Latino | 3 (15.8%) | 6 (35.3%) |
| | Not Hispanic or Latino | 16 (84.2%) | 11 (64.7%) |
| Mental retardation – present | | 19 (100%) | 17 (100%) |
| Speech impairment – present | | 19 (100%) | 17 (100%) |
| Oral feeding problems | Present | 10 (52.6%) | 8 (47.1%) |
| | Absent | 9 (47.4%) | 9 (52.9%) |
| Uses tube for feeding | Yes | 7 (36.8%) | 8 (47.1%) |

| | | Glycopyrrolate oral solution (n=19) | Placebo (n= 17) |
|---|---|---|---|
| | No | 12 (63.2%) | 9 (52.9%) |
| Residence of patient | With parent | 17 (89.5%) | 16 (94.1%) |
| | With foster parent/guardian | 2 (10.5%) | 1 (5.9%) |
| History of glycopyrrolate use | Yes | 3 (15.8%) | 3 (17.6%) |
| | No | 16 (84.2%) | 14 (82.4%) |

No significant differences are observed in the baseline characteristic.

**Numbers analysed**

In the glycopyrronium group 19 subjects were analysed for efficacy out of 20 randomised subjects. The corresponding figures for the placebo group were 17 and 18 subjects, respectively. This modified intent-to-treat (mITT) analysis excluded the two subjects with an age between 17 and 23 years randomised prior to an amendment of the protocol that restricted the study population age to 3-16 years.

**Outcomes and estimation**

Primary endpoint

The responder rate at Week 8 for the primary endpoint (≥ 3 point improvement on the mTDS) was significantly higher for Cuvposa (14/19; 73.7%) than for placebo (3/17; 17.6%) (p = 0.0011, Fisher's exact test), with improvements starting 2 weeks after treatment initiation (52.6% vs. 0%; p=0.00007) (Figure 1).

Secondary efficacy endpoints

Mean improvements in mTDS score at week 8 were 3.94 points (SD: 1.95, 95% confidence interval [CI]: 2.97–4.91, median: 4.30 points) in the glycopyrrolate oral solution group and 0.71 points (SD: 2.14, 95% CI: –0.43–1.84, median: 0.25 points) in the placebo group (P<0.0001).

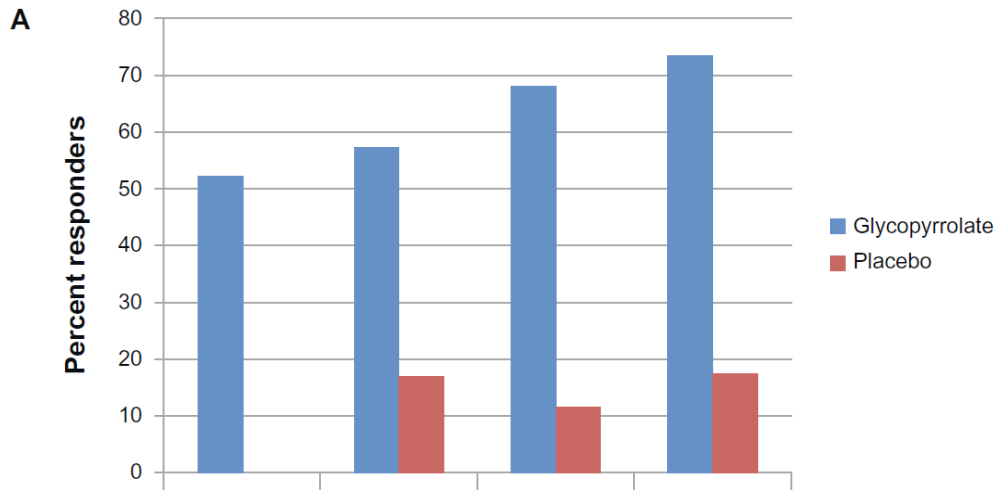
After 8 weeks treatment mean scores on the mTDS approximated to the descriptors "mild; only the lips are wet, but frequently" in the Cuvposa arm compared with the mid-point of "moderate; wet on the chin frequently" and "severe; drooling to the extent that clothing becomes damp occasionally" in the placebo arm.

In total, 84.2% of Investigators and 100% of P/C regarded Cuvposa as worthwhile compared with 41.2% (p = 0.0140; Fisher's exact test) and 56.3% (p = 0.0017), respectively, for placebo.

**Ancillary analyses**

A clinically relevant beneficial effect of Cuvposa was observed as early as 2 weeks after treatment initiation; in the publication, 52.6% in the Cuvposa arm were stated to be responders at this timepoint (vs. 0% in the placebo group; p=0.00007) (Figure 1).

**Figure 1: Proportion of responders by treatment group in Zeller *et al*, 2012a, defined as ≥ 3 point improvement in mTDS score**

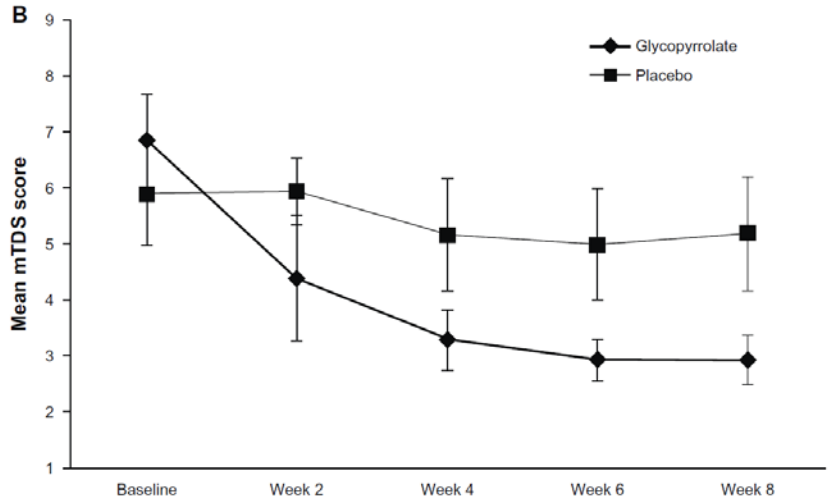



| | Week 2 | Week 4 | Week 6 | Week 8 |
|---|---|---|---|---|
| Glycopyrrolate | 52.6 | 57.9 | 68.4 | 73.7 |
| Placebo | 0 | 17.6 | 11.8 | 17.6 |

Note: In reporting the results of this study, the authors of the publication used the US Approved Name for GP, i.e. glycopyrrolate.

Consistent with the primary endpoint of responder rate, the mean mTDS score also improved (decreased) over time. The difference between GP and placebo reached the level of statistical significance by Week 4. By Week 8, a highly significant difference in mTDS between the two treatment arms was observed ($p<0.0001$).

**Figure 2: Mean mTDS scores (± 2 SEMs) over time to Week 8**




| | | | | | |
|---|---|---|---|---|---|
| Glycopyrronium bromide | 7 | 4.4 | 3.3 | 3.1 | 3.1 |
| Placebo | 5.8 | 5.9 | 5.2 | 5.3 | 5.4 |

Data source: Zeller, 2012a.
Key: SEM = standard error of mean

Seventeen out of 19 subjects (89.5%) in the GP arm completed the study. The mean duration of Cuvposa exposure was 55.4 days. Mean daily dose of Cuvposa was 0.15 mg/kg (0.05 mg/kg tid); 68% of subjects

had a daily dose from 0.1 mg/kg to 0.2 mg/kg; ten of the seventeen subjects who completed the trial reached the highest dose level for baseline weight (i.e. 0.3 mg/kg or 9 mg, whichever was less). There were 56 up and 11 down titrations.

In the placebo group 15/17 (88.2%) completed the study; a larger proportion (14/17; 82.3%) were on the highest dose level. There were 67 up and 3 down titrations.

One subject in the placebo arm discontinued the study due to lack of efficacy; there were no discontinuations due to lack of efficacy in the GP arm.

### Mier *et al 2010*. Study title: Treatment of sialorrhoea with glycopyrrolate. A double-blind, dose-ranging study.

A placebo controlled cross-over study with two sequences each containing two treatment periods (either capsules glycopyrrolate or capsules placebo for eight weeks) in developmentally disabled children with sialorrhoea.

#### *Methods*

#### *Study Participants*

Children aged 4 years and older, with neurodevelopmental conditions and severe sialorrhoea, were recruited. The admission criteria allowed previous treatment with medication against drooling (glycopyrrolate inclusive).

#### *Treatments*

Different GP dosing schemas were used based upon the weight of subjects at baseline with dosing based upon ter in die (tid) administration (Table below).

**Table 10: Dosing schema in Mier *et al***

| | Dose (mg) | | | |
|---|---|---|---|---|
| **baseline weight** | **Week 1 (Level 1)** | **Week 2 (Level 2)** | **Week 3 (Level 3)** | **Week 4 (Level 4)** |
| <30 kg | 0.6 (>0.02 mg/kg) | 1.2 (>0.04 mg/kg) | 1.8 (>0.06 mg/kg) | 2.4 (>0.08 mg/kg) |
| >30 kg | 1.2 (<0.04 mg/kg) | 1.8 (<0.06 mg/kg) | 2.4 (<0.08 mg/kg) | 3.0 (<0.1 mg/kg) |

Data source: Mier, 2000

Note: The mean highest tolerated dose of GP among the 27 children who completed the study was 2.49 mg per dose (range 1.2 – 3.0 mg). The mean highest tolerated dose of GP per kilogram body weight was 0.11 mg/kg per dose (range: 0.04 – 0.2 mg/kg).

Doses were increased weekly for 4 weeks to a maximum dose, which was then continued for an additional 4 weeks. Doses were increased according to this schedule unless adverse events (AEs) occurred or unless desired dryness, as defined by the P/C, was obtained.

Oral GP was administered as a crushed and encapsulated (gelatin) presentation, which had been prepared extemporaneously by the study pharmacist by crushing commercially available Robinul tablets. Otherwise

identical placebo gelatin capsules contained lactose powder or cellulose. These procedures were necessary to maintain the treatment blinding, since placebo tablets were not available. P/C of children who were unable to swallow the capsules were instructed to take the capsule apart and place the powdered contents in the child's food. Otherwise, no specific recommendations were given with regard to timing of medication and food.

After an initial 1 week baseline medication free observation period, subjects were randomized to either GP or placebo, each for an 8 week treatment period. At the end of the first period there was a 1 week washout, followed by a second week long observation period, then followed the reciprocal treatment arm, also 8 weeks long. Each treatment period contained a four-weeks titration phase and a four-weeks maintainance phase. Titration was done in weekly fixed steps (different doses per kg body weight depending on body weight above or under 30 kg) up to an individualized therapeutic optimal dose.

***Objectives***

To determine the safety and efficacy of glycopyrrolate in the treatment of developmentally disabled children with sialorrhoea.

***Outcomes/endpoints***

Drooling was evaluated by P/C using the mTDS. A set of cartoon illustrations was used to educate parents about this scale and was provided to them for home use. Drooling scores were obtained during the baseline observation periods and through weekly telephone calls to the parents by a research assistant. All scores were obtained in the afternoon, 2 hours after a dose.

Caretakers were also asked to assess drooling and dryness of clothing.

***Sample size***

Thrirty-nine children began the study and 27 children completed it.

***Randomisation***

No details about the randomisation are provided.

***Blinding (masking)***

Because placebo tablets identical to commercially available glycopyrrolate were not available, capsules were specially compounded by a pharmacist, who ground up commercially available glycopyrrolate tablets and placed the required amount of powder into gelatin capsules.

***Statistical methods***

Tests of statistical significance included the paired, 2-tailed t test and the unpaired t test. Testing for statistical significance was only done for subjects who completed the study and with respect to mean treatment changes on mTDS.

***Results***

**Participant flow**

Thirty-nine children began the study, and 27 children (69%) completed it. Of the 12 children who did not complete the study, 8 dropped out because of adverse effects to medication, 1 of these while receiving placebo. Four children were dropped because of failure to comply with the protocol or because it was inconvenient for their families to continue. The 4-months study was completed by 18 boys and 9 girls (Table below).

**Table 3. Glycopyrrolate Study Summary**

| Characteristic | |
|---|---|
| No. of patients enrolled | 39 |
| No. of patients completing study | 27 |
| No. of patients who withdrew because of adverse effects to glycopyrrolate | 7 |
| No. of patients who withdrew for other reasons | 5* |
| Mean highest tolerated dose, mg/kg | 0.11 |
| Range of highest tolerated dose, mg/kg | 0.04-0.20 |

**One patient dropped out because of adverse effects while receiving placebo; 4 patients were dropped because of problems keeping appointments or problems using study medication as prescribed.*

**Recruitment**

The trial was conducted during the period 1998-1999.

**Conduct of the study**

Subjects were recruited at two identified sites in the USA. These two sites were outpatient facilities in paediatric hospitals. The trial most likely followed the principles of the Declaration of Helsinki. Whether the trial followed the GCP rules applicable at that time could not be clarified.

**Baseline data**

Ages at enrollment ranged from 4 years 4 months to 19 years, with a mean age of 10 years 9 months. Thirty-four children had cerebral palsy; 1 each had Smith-Lemli-Opitz syndrome, closed head injury, partial trisomy 22, congenital toxoplasmosis, and spinal muscular atrophy. Eleven children had additional medical conditions, most commonly a seizure disorder (6 children) but also including autism, fetal alcohol syndrome, hydrocephalus, congenital heart disease, hypothyroidism, and retinitis pigmentosum. Two children had tracheostomies, 1 of whom dropped out of the study because of excessively thick secretions. Five children had been previously treated for their drooling with medication, 3 of whom had taken glycopyrrolate but stopped because of adverse effects. Weights at enrolment ranged from 11.5 kg to 61.9 kg.

**Numbers analysed**

In total 27 (of 39) subjects (69%) completed the cross-over study. No subject was withdrawn due to lack of efficacy. Only subjects completing the study were included in the efficacy analyses.

**Outcomes and estimation**

Primary endpoint

The mean baseline drooling score improved with glycopyrrolate from 7.52 to a maximum mean score of 1.85. A mean score of 1.85 corresponds to a description between “dry, never drools” and “mild drooling; only the

lips are wet occasionally." With placebo, the baseline score improved slightly from 7.44 to 6.33. Mean drooling score on glycopyrrolate (1.85) compared with placebo (6.33) is statistically different, with P<.001.

**Ancillary analyses**

Drooling scores improved with increasing dose in a linear manner. The mean score for children finishing the study was 6.0 on their first dose level, 4.5 on the second dose level, 3.6 on the third dose level, 2.6 on the fourth dose level, and 2.3 after 4 weeks at their highest dose.

Using an improvement-in-drooling score of 4 points or greater as a standard for significant clinical improvement, 12%, 38%, 54%, and 81% of study participants met this standard on the first, second, third, and fourth dosing levels, respectively (Figure below).

**Figure 3**

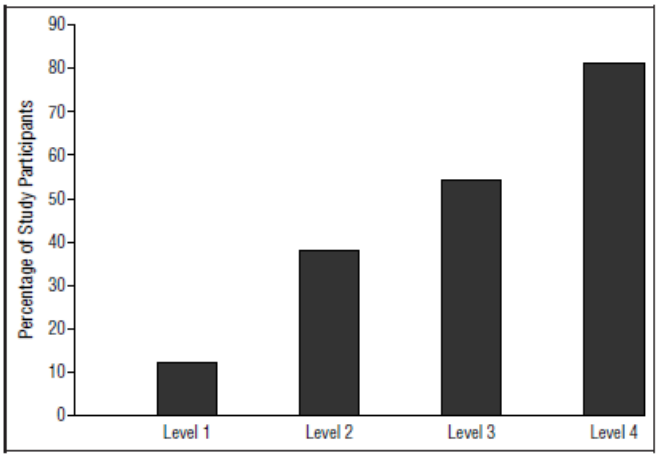



**Figure 1.** *Percentage of study participants who improved drooling score by 4 points or more at each dosage level.*

The children were maintained at their highest tolerated dose for 4 weeks to determine if drug effects changed during that period; the drooling score improved in 9 children, decreased in 9, and remained the same in 9.

Six (22%) of the 27 children who completed the study achieved their best drooling score while receiving doses lower than their fourth dosing level. Four of these 6 reached their best score 1 dosing level below their highest tolerated level. One child reached the best drooling score 2 dosing levels below the highest tolerated level, and another child reached the best score on the first dosing level.

Of the caretakers who responded, 15 (65%) of 23 reported that their child exhibited less drooling odor while receiving glycopyrrolate compared with the placebo, and 21 (87%) of 24 caretakers reported improved dryness of clothing compared with placebo.

The mean highest tolerated dose of glycopyrrolate among the 27 children who completed the study was 2.49 mg, with a range from 1.2 mg to 3.0 mg per dose. The mean highest tolerated dose of glycopyrrolate per kilogram of body weight was 0.11 mg/kg per dose, with a range from 0.04 mg/kg to 0.2 mg/kg per dose.

**Summary of main studies**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 11 Summary of Efficacy for Zeller 2012a**

| | | | |
|---|---|---|---|
| **Title**: 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 | | | |
| Study identifier | Zeller et al. Therapeutics and Clinical Risk Management 2012;8:15–23 | | |
| Design | Randomised, double-blind, placebo-controlled, parallel-group efficacy and safety study. 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 glycopyrrolate (n = 20), 0.02–0.1 mg/kg three times a day, or matching placebo (n = 18). | | |
| | Duration of main phase:<br><br>Duration of Run-in phase:<br><br>Duration of Extension phase: | | 8 weeks (including 4-week titration)<br><br>2 weeks (no anti-sialogenic, anticholinergic or cholinergic medicines allowed) |
| Hypothesis | Superiority to placebo for responder rate. | | |
| Treatments groups | Glycopyrrolate oral solution | | During the first 4 weeks, doses were titrated weekly to the optimal tolerated response for each study participant, but not exceeding 1.5–3.0 mg per dose based on weight, with the optimal tolerated dose reached by week 4. Five dose levels (0.02 mg/kg three times a day, 0.04 mg/kg three times a day, 0.06 mg/kg three times a day, 0.08 mg/kg three times a day, and 0.1 mg/kg three times a day). After the optimal dose level was reached, patients continued to receive the same medication and dose, for a total of 8 weeks. Number = 19 |
| | Placebo - Matched | | Identical to the above. Number = 17 |
| Endpoints and definitions | Primary Endpoint | | Responder rate, defined as percentage showing ≥3-point increase on the modified Teacher's Drooling Scale (mTDS). |

| | | | |
|---|---|---|---|
| | Secondary endpoint - efficacy | | • Daily mean parent/ caregiver mTDS scores at weeks 2, 4, and 6<br>• AUC analysis of all mTDS evaluations from screening to week 8<br>• Proportion of patients who discontinued treatment due to lack of efficacy<br>• Global assessments by the parent/caregiver, by patients deemed cognitively capable by the investigator, and by physicians, performed at week 8 or at the last visit, using a 5-point scale, ranging from 1 (strongly agree) to 5 (strongly disagree) in response to the statement “This is a worthwhile treatment”<br>• Assessments using a modified Behavioral and Medical Rating Scale (mBMRS)<br>• Tabulation and description of all AEs<br>• Effectiveness of the training manual |
| | Secondary endpoint - safety | | Safety was evaluated by physical examination, 12-lead ECG, clinical laboratory test results and urinalysis. Assessed at baseline and at week 8 or study discontinuation. |
| Database lock | Not Available | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | A modified intention-to-treat population encompassing all randomized patients who received at least one dose of study medication and were within the amended age range (3-16 years). | | |
| Descriptive statistics and estimate variability | Treatment | Glycopyrronium | Placebo |
| | Number of subjects | 19 | 17 |
| | mTDS, proportion with ≥3-point improvement in mTDS at week 8 | 73.7% | 17.6% |
| | mTDS, mean improvement in mTDS at week 8 | 3.94<br>SD: 1.95 | 0.71<br>SD: 2.14 |
| | Investigator global assessment, proportion rated as worthwhile | 84.2% | 41.2% |
| | Patient/caregiver global assessment, proportion rated as worthwhile | 100% | 56.3% |
| Effect estimate per comparison | mTDS, proportion with ≥3-point improvement | Comparison groups | Glycopyrronium vs. placebo |

| | | | |
|---|---|---|---|
| | in mTDS at week 8 | Difference | 56.1% |
| | | p-value | 0.0011 |
| | mTDS, mean improvement at week 8 | Comparison groups | Glycopyrronium vs. placebo |
| | | Difference | 3.23 |
| | | p-value | < 0.0001 |
| | Investigator global assessment, proportion rated as worthwhile | Comparison groups | Glycopyrronium vs. placebo |
| | | Difference | 43.0% |
| | | p-value | 0.0140 |
| | Patient/caregiver global assessment, proportion rated as worthwhile | Comparison groups | Glycopyrronium vs. placebo |
| | | Difference | 43.7% |
| | | p-value | 0.0017 |
| Notes | None. | | |
| **Analysis description** | **Secondary analysis** | | |
| | Only efficacy analyses using the mITT population are presented in article. | | |

**Table 12 Summary of Efficacy for Mier et al, 2000**

| **Title**: Treatment of Sialorrhoea With Glycopyrrolate - A Double-blind, Dose-Ranging Study | | |
|---|---|---|
| Study identifier | Mier et al. Arch Pediatr Adolesc Med. 2000;154:1214-1218 | |
| Design | Randomised, double-blind, placebo-controlled, crossover, dose-ranging efficacy and safety study.<br><br>After an initial physical evaluation and a 1-week baseline medication-free observation period, each child was assigned randomly to either the drug or placebo treatment arm, each of which was 8 weeks long. At the end of the first arm, there was a 1-week washout period and a second week-long observation period, followed by the reciprocal arm, also 8 weeks in length. | |
| | Duration of main phase:<br><br>Duration of Run-in phase:<br><br>Duration of Extension phase: | Not Available<br><br>Not Applicable<br><br>Not Applicable |
| Hypothesis | Superiority to placebo for reduction in drooling. | |

| | | | |
|---|---|---|---|
| Treatments groups | Treatment - glycopyrrolate Specially compounded capsules using ground up commercially available glycopyrrolate tablets in gelatin capsules. | | Two dosage regimens were used based on the weight category of the child: children weighing less than 30 kg began at 0.6 mg, increasing weekly to 1.2 mg, 1.8 mg, and 2.4 mg. Children weighing more than 30 kg began by taking 1.2 mg, increasing weekly to 1.8 mg, 2.4 mg, and 3.0 mg. |
| | Placebo - Lactose powder or cellulose prepared similarly, using identical gelatin capsules. | | Identical to the above. |
| Endpoints and definitions | Primary Endpoint | | Drooling score |
| | Secondary endpoint - efficacy | | • Drooling score, mean score after 4 weeks at highest dose by dose level<br>• Drooling score, proportion with ≥4-point improvement by dose level<br>• Caretaker assessment of drooling odour<br>• Caretaker assessment of dryness of clothing |
| | Secondary endpoint - safety | | Safety was evaluated by assessment of AEs |
| Database lock | Not Available | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | The 27 children who completed the study were analysed. | | |
| Descriptive statistics and estimate variability | Treatment | Glycopyrronium | Placebo |
| | Number of subjects | 27 | 27 |
| | Drooling score, mean score following treatment | 1.85 | 6.33 |
| | Drooling score, mean score after 4 weeks at highest dose by dose level | Level 1: 6.0<br>Level 2: 4.5<br>Level 3: 3.6<br>Level 4: 2.3 | - |
| | Drooling score responder, proportion with ≥4-point improvement at week 8 | Level 1: 12%<br>Level 2: 38%<br>Level 3: 54%<br>Level 4: 81% | - |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Drooling score, mean score after 8 weeks' treatment | Comparison groups | Glycopyrronium vs. placebo |
| | | Difference | 4.48 |
| | | p-value | 0.0011 |
| Notes | None. | | |
| **Analysis description** | **Secondary analysis** | | |
| | No other analysis datasets were presented in article. | | |

**Analysis performed across trials (pooled analyses and meta-analysis)**

The applicant provided broad description of studies Zeller 2012a , Mier et al, 2000 and Zeller et al 2012 as an analysis across the trials. Results of these studies were not statistically analysed (not possible to compare due to methodological differences) and therefore there are no new results presented. Therefore the assessment is the same as for efficacy results for single studies.

**Clinical studies in special populations**

No clinical studies in special populations were submitted by the Applicant which was considered acceptable by the CHMP.

**Supportive studies**

The four published supportive studies are summarised below.

**Zeller *et al* 2012. Study title: Safety and efficacy of glycopyrrolate oral solution for management of pathologic drooling in pediatric patients with cerebral palsy and other neurologic conditions.**

Background: The purpose of this study was to assess the safety and efficacy of oral glycopyrrolate solution 1 mg/5 mL for 24 weeks in pediatric patients with chronic moderate to-severe drooling associated with cerebral palsy and other neurologic conditions.

Methods: In this multicenter, open-label, 24-week study, males and females aged 3–18 years weighing at least 27 lb received oral glycopyrrolate solution, starting at 0.02 mg/kg three times daily and titrated in increments of 0.02 mg/kg every 5–7 days for 4 weeks to an optimal maintenance dose or a maximum dose of 0.1 mg/kg, but not exceeding 3 mg three times daily. Safety was assessed by description and tabulation of all adverse events. The primary efficacy endpoint was response, defined as at least a three-point change from baseline to week 24 on the modified Teacher's Drooling Scale.

Results: One-hundred and three subjects out of 137 (75%) subjects completed the study; 2 subjects withdrew for lack of efficacy.

The mean daily dose of Cuvposa was 0.15 mg/kg; 51% of subjects received a mean daily dose ≥ 0.1 mg/kg to ≤ 0.2 mg/kg, while 7% of subjects received the maximum dose (0.1 mg/kg tid). Mean duration of exposure was 139.8 days, 76% of subjects had exposure >150 days to ≤ 200 days. Over 24 weeks, 45% of subjects had a dose reduction.

At Week 24, 52.3% (95% CI 43.7–60.9) of subjects were responders (≥ 3 point reduction on the mTDS). The proportion of responders ranged between 40.3% and 56.7% over the 6 assessment points during the 24

week study period. A higher proportion of non GP naïve subjects (n=53) were responders compared with GP naïve subjects (n=84) (59%; 95% CI 45.2-71.8 vs. 48%; 95% CI 36.9- 59.2).

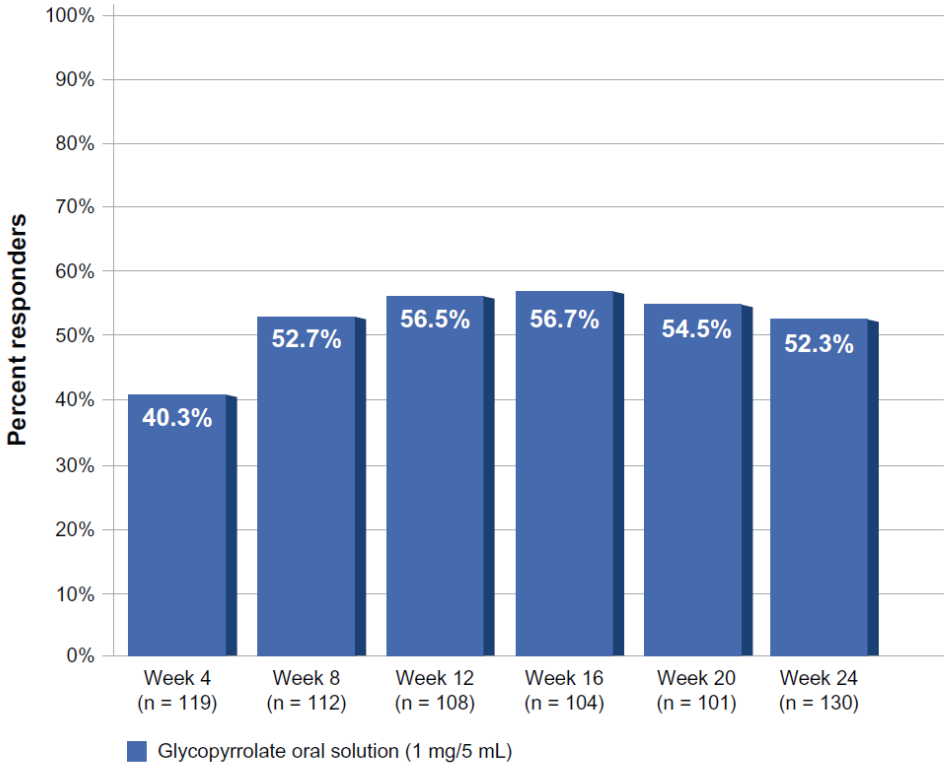



**Figure 1** Proportion of responders after 4–24 weeks of treatment with oral glycopyrrolate solution 1 mg/5 mL. Response was defined as at least a three-point decrease c the Modified Teachers' Drooling Scale. The percentage of responders at each time point from week 4 to week 20 was assessed relative to the number of patients remainir on study at that time point. The percentage of responders at week 24 was assessed relative to all intent-to-treat patients (n = 137), except for seven patients with missir values. Patients who discontinued treatment due to lack of efficacy had their worst observation carried forward, whereas patients who discontinued due to any other reaso had their last observation carried forward.

The proportions of subjects with profuse, severe, and moderate drooling decreased substantially from baseline to Week 24: 32% to 2%, 37% to 8%, and 32% to 26%, respectively. By Week 24, 15% of subjects were non-droolers.

P/C assessed improvement in their child's drooling on a Visual Analogue Scale (VAS) (0-10 cm); the mean score improved from 6.56 at baseline to 3.21 at Week 24. In total, 83.5% of P/C and 85.8% of investigators rated Cuvposa as being a worthwhile treatment.

**Stern 1997. Study title: Preliminary study of glycopyrrolate in the management of drooling**

Objective: A study was undertaken to assess the efficacy of an oral anticholinergic drug, glycopyrrolate, in the management of drooling in children and young adults with disabilities.

Methodology: Glycopyrrolate was used once daily by 24 children and young adults for up to 28 months. Parents/carers were asked to complete a questionnaire on the effects of the drug on severity and frequency of drooling and to report any side-effects.

Results: The dose titration scheme for GP was in the range 0.04 – 0.1 mg/kg/day with a maximum dose of 0.175 mg/kg/day; the lower dose was used to initiate therapy and the dosage increased until a significant

decrease or cessation of drooling occurred. No information about final dose was given in the publication. The majority of the 22 subjects with data (out of 24) were reported to have shown improvement in both severity and frequency of drooling; no further details were provided. The results, analysed using Wilcoxon signed rank analysis, were highly significant: for severity Z=3.6214; p=0.0003; for frequency Z=2.7064; p=0.0068).

**Blasco *et al* 1996. Study title: Glycopyrrolate treatment of chronic drooling**

Objective: To describe the use of glycopyrrolate in the control of drooling in children and young adults with cerebral palsy and related neurodevelopmental disabilities.

Design: Prospective, open-label study of drug dosage parameters, response to therapy, and side effects. Follow-up ranged from 8 months to 4 years.

Setting: Outpatient clinic of a rehabilitation hospital that is a regional referral center for children with disabilities.

Patients: Forty children and young adults with motor and/or cognitive disabilities who were experiencing drooling to a severe degree.

Intervention: Treatment with oral glycopyrrolate.

Outcome Measures: Change in the quantity of drooling and side effects associated with treatment.

Results: Thirty-six patients (90%) had reduced drooling in response to medication; 2 (5%) could not be assessed and 2 (5%) received no benefit. Side effects resulted in discontinuation of treatment in 11 (28%). Overall, 26 (65%) continued to receive drug therapy because of the perceived benefit. The final effective dose ranged widely from 0.01 to 0.82 mg/kg per day.

**Arbouw *et al* 2010. Study title: Glycopyrrolate for sialorrhoea in Parkinson disease. A randomized, double-blind, crossover trial**

Background: Sialorrhoea affects approximately 75% of patients with Parkinson disease (PD). Sialorrhoea is often treated with anticholinergics, but central side effects limit their usefulness. Glycopyrrolate (glycopyrronium bromide) is an anticholinergic drug with a quaternary ammonium structure not able to cross the blood-brain barrier in considerable amounts. Therefore, glycopyrrolate exhibits minimal central side effects, which may be an advantage in patients with PD, of whom a significant portion already experience cognitive deficits.

Objective: To determine the efficacy and safety of glycopyrrolate in the treatment of sialorrhoea in patients with PD.

Methods: A 4-week, randomized, double-blind, placebo-controlled, crossover trial with oral glycopyrrolate 1 mg 3 times daily in 23 patients with PD. Treatment with either glycopyrrolate or placebo was one week each. The severity of the sialorrhoea was scored on a daily basis by the patients or a caregiver with a sialorrhoea scoring scale ranging from 1 (no sialorrhoea) to 9 (profuse sialorrhoea).

Results: Both primary (p=0.021) and secondary (p=0.011) outcome measures of sialorrhoea improved with glycopyrrolate compared with placebo. For the primary endpoint, nine of 23 patients (39.1%) responded to glycopyrrolate vs 1 of 23 patients to placebo (4.3%; difference in responder rate 34.8%, bootstrap 95% CI 13.0%–56.5%). The mean improvement in sialorrhoea score with glycopyrrolate compared with placebo was 0.8 points (bootstrap 95% CI 0.02–1.4 points). One patient inadvertently used 5 times the prescribed volume during 3 days in the first week of trial medication, in which he had been using glycopyrrolate. In the

per-protocol analysis, with exclusion of this patient, the primary outcome did not change. The secondary outcome measures in the per-protocol analysis were as follows: mean (SD) sialorrhoea score 4.7 (1.7) with placebo vs 3.9 (1.6) with glycopyrrolate (p=0.015).

**Mapping exercise to estimate utility values for drooling in cerebral palsy (QoL Mapping)**

**Chang et al. 2012** was a study to investigate the association between drooling in children with cerebral palsy and their health-related quality of life (HRQOL), as well as the possible variables that predict their HRQOL. Children with CP, without other identified disease, aged 2 to 6 years, who drool (n = 33) or did not drool (n = 14), were included. The dependent variables were the physical health summary scores and the psychosocial health summary scores of the Pediatric Quality of Life Inventory version 4.0.
Results: The physical health and psychosocial health summary scores of the children that drooled (16.29 ± 15.97 and 42.92 ± 17.57, respectively) were lower than for the children that did not drool (31.97 ± 22.22 and 57.09 ± 12.21, respectively; P , 0.01). The drooling ranking score was negatively correlated with the physical health summary score (r = −0.355; P , 0.05) and the psychosocial health summary score (r = −0.381; P , 0.01). The stepwise regression showed that gross motor development and the drooling ranking score predicted 56.6% of the variability of the physical health summary score (R2 = 0.566; P , 0.01). The language development score predicted 25.6% of the variability of the psychosocial health summary score (R2 = 0.256; P , 0.01).
Drooling was associated with a lower HRQOL. Prediction of the physical health summary score was more closely associated with gross motor development and the drooling ranking scores.

**Khan et al. 2014** assesses different mapping methods for estimating EQ-5D health utilities from PedsQL™ GCS responses.

The primary objectives of this exercise were to:

- Estimate EQ-5D utilities from the Pediatric Quality of Life questionnaire v4 (PedsQL) based on the Khan et al., (2014) mapping algorithm using a Taiwanese dataset provided, and previously described and published, by Chang et al., (2012).
- Generate descriptive statistics for the estimated utility scores across the following drooling groups based on the Drooling Rating Scale (DRS) data included in the Chang et al, dataset:
- Drools vs. never drools (A proxy of the Modified Teachers Drooling Scale (mTDS) including the categories: never drools, mild/moderate drooling and severe/profuse drooling)

Methods

Patient level PedsQL domin scores (Physical, Emotional, Social and School, Functioning) were provided by the authors of Chang et al. 2012 and were utilized to derive all the variables required to estimate EQ-5D utilities based on the Khan et al., mapping algorithm.

In other words, utility scores were estimated from the Chang et al. PedsQL data using the published coefficients in the following algorithm:

***Utility*** *= -0.428496 + (Physical function (PF) * 0.009127) +(Emotional function (EF) * 0.006611) + (Social function (SF) * 0.005705) + (School function (SchF) * 0.006011) + ($PF^2$ * 0.000020) - ($EF^2$ * 0.000048) + ($SF^2$ * 0.000011) - ($SchF^2$ * 0.000017) - (PFxEF * 0.000004) - (PFxSF * 0.000055) - (PFxSchF * 0.000066) - (EFxSF * 0.000009) + (EFxSchF *0.000059) - (SFxSchF * 0.000027)*

Drooling groups

It was possible to define drooling groups, using the drooling rating scale patient level data provided by the authors of the Chang et al. paper. By defining drooling groups it was then possible to estimate health state utilities for each drooling group. The drooling rating scale has a score ranging from 2 to 9 based on the sum of drooling severity and drooling frequency as outlined in the table below:

| Drooling Severity | Drooling Frequency |
|---|---|
| 1. Never drools | 1. Never |
| 2. Mild (wet lips) | 2. Occasionally |
| 3. Moderate (wet lips & chin) | 3. Frequently |
| 4. Severe (wet clothing) | 4. Constantly |
| 5. Profuse (clothing, hands etc., wet) | |

For the assessment of Never Drools vs Drools, a score 2 was classified as Never Drools and a score > 2 as Drools.

For the proxy truncated mTDS groups: Never drools was defined as before, Mild/Moderate Drooling included DRS severity scores of 2/3 combined with any frequency score > 1, and Severe/Profuse Drooling included DRS severity scores of 4/5 combined with any frequency score >1.

Categorical groups of the DRS and a truncated version of the mTDS were used since the sample size in the dataset was known a priori to be too small (n=47) to consider all eight DRS categories and all nine mTDS groups.

Results and Discussion

From the original sample, a total of 31 subjects had sufficiend PedsQL data to enable the estimation of utility scores. The main reason utility could not be estimated was due to missing School Functioning domain scores.

Hence the Never Drools vs. Drools utility values summarized in Table 2 include a sample of n=31. The utility data presented by truncated mTDS groups in Table below, includes n=30, as one subject did not provide sufficient data to be categorized into the mTDS proxy group.

**Table 13**

Table 2 Utility descriptive statistics by 'Never Drools' vs. 'Drools' categories

| Statistic | Never Drools | Drools |
|---|---|---|
| N | 7 | 24 |
| Mean | 0.500 | 0.258 |
| Standard Deviation | 0.139 | 0.235 |
| Min - Max | 0.301 - 0.650 | - 0.218 - 0.708 |
| Standard Error of Mean | 0.052 | 0.048 |
| 95% CI | 0.398 - 0.602 | 0.164 – 0.352 |

Table 3 Utility descriptive statistics by proxy truncated mTDS groups

| Statistic | Never Drools | Mild/Moderate | Severe/Profuse |
|---|---|---|---|
| N | 7 | 17 | 6 |
| Mean | 0.500 | 0.313 | 0.113 |
| Standard Deviation | 0.139 | 0.230 | 0.223 |
| Min - Max | 0.301 - 0.650 | - 0.218 - 0.708 | -0.148 - 0.378 |
| Standard Error of Mean | 0.052 | 0.056 | 0.091 |
| 95% CI | 0.398 - 0.602 | - 0.203 – 0.423 | -0.065 – 0.291 |

The group means show a monotonic relationship between drooling and utility indicating decreased utility (decreased health related quality of life) with increased drooling.

## 2.5.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

No dose response studies within the clinical efficacy data package were provided; instead analysis of clinical information relevant to dosing recommendation was presented.

Dose titration is recommended in current drug formularies and the main treatment reference texts in UK including the British National Formulary for Children and the Association of Paediatric Palliative Medicine. An on-going clinical trial of another oral solution presentation of GP is using the APPM dose titration recommendations (Parr, 2014; EudraCT: 2013-000863-94): 40 µg/kg initial dose with 20 µg/kg increases to 100 µg/kg in Week 4, with a maximum individual dose of 2 mg (equivalent to 0.2 mg/kg at the smallest eligible weight [10 kg]).

There are no dedicated dose-finding studies or multiple-dose pharmacodynamic studies, which would identify appropriate dose. The therapeutic dose-range therefore has to be inferred from the two main studies and particularly from the study by Zeller 2012a.

Data from a comparative BA study conducted by the Applicant in healthy adults indicate that the proposed product, GBOS (0.4 mg/mL [Sialanar]) is approximately 25% more bioavailable than Cuvposa on average

(based on AUC(o-t)). Maximum exposure (Cmax) after a single 2 mg dose of GBOS (0.4 mg/mL) is approximately 21% higher than after the same dose of Cuvposa.

The significant difference in bioavailability between the two formulations was a major concern to the CHMP because one could question the originally proposed initial dose and dose titration schedule for GBOS (which was identical to that of Cuvposa) both with regard to efficacy and safety. However, the recommended schedule has been revised so that it no longer is a copy of the one adopted for Cuvposa in the US, but instead applies a 20% lower initial dose and 20% lower dose increments reflecting that the exposure following GBOS is approximately 20-25% higher than following Cuvposa. Hence, the exposure levels during titration of GBOS would largely mirror those obtained during titration of Cuvposa. The revised titration schedule earlier proposed by the Applicant is considered the only appropriate solution when considering the markedly higher exposure of GBOS as compared to Cuvposa and is thus acceptable.

Main study Zeller 2012a

In the absence of regulatory guidelines, the claimed design of this study is adequate for the purpose of demonstrating short-term efficacy. The Applicant clarified during the procedure that the trial most likely had a double-blind design. The study population with a lowest age limit of three years does not support the originally proposed SmPC with a lower age limit of two years, otherwise the study population was adequately selected. However, the Applicant proposed in the course of the procedure to limit the lowest age in the indication to be three years which is acceptable. The eligibility criteria allowed previous use of GP, which theoretically could bias internal and external validity. However, since quite few subjects had previous GP use and were balanced between the treatment groups this is not likely that previous use of GP in the Zeller 2012a study did bias the study results. The use of placebo as the only comparator is supported since no other anti-sialorrhoea product has been extensively authorised in the EU. The choice of mTDS as the primary outcome measurement is also supported and using it for a responder analysis (with a responder representing a ≥3 points improvement) as the primary endpoint and mTDS mean change as a secondary endpoint is further endorsed.

The CHMP questioned whether the 8-weeks treatment duration is sufficient to support chronic use of GP. Only one long-term published article of a sufficient study design for safety evaluation, Zeller 2012b, has been presented and this was only a 24-week non-comparative study with 137 patients. The efficacy results from a trial with such a design are only indicative of long-term efficacy.

Therefore a description of the study was included in 5.1 of the SmPC and a statement that Placebo controlled efficacy data includes patients with treatment duration of 8 weeks. There is no placebo or comparator controlled data beyond 8 weeks. Furthermore it was included that there is insufficient data beyond 24 weeks to establish the long-term efficacy and safety profile of glycopyrronium in the target population. The recommended maximum duration of therapy is 24 weeks.

Fisher´s exact test is an appropriate statistical test method for the primary endpoint. An estimate of the variation, e.g. a bootstrapped 95% confidence interval, should preferably also have been included in the statistical test methods of the primary endpoint. The Applicant has in its response clarified that such an estimate of the variation is not possible to provide due to lack of access to raw data. The scheduling of the IMP dosing with a standardised time window before and after intake of meal was appropriate.

The study was conducted according to GCP.

The reporting of the results has limitations which are the usual inherent with a bibliographic application.

Main study Mier 2010

In the absence of regulatory guidelines, the design of this study is also adequate for the purpose of demonstrating short-term efficacy. The study population with a lowest age limit of four years does not support the proposed SmPC with a lower age limit of originally two years, now revised to three years. The study population was not extensively described. Also in this trial, the eligibility criteria allowed previous use of GP, which theoretically could bias internal and external validity. Since only five subjects were previously treated with GP, the Applicant has in its response made it probable that this potential bias was most likely limited. The use of placebo as the only comparator is once again supported since no other anti-sialorrhoea product has been extensively authorised in the EU. The choice of mTDS as the presumed primary outcome measurement is also supported and supposedly using it for the primary endpoint mTDS mean change is further endorsed. However, as with Zeller 2012a main study, one certainly can question if the 8-weeks treatment duration is sufficient to support chronic use of GP and as already mentioned the Applicant has now in the PI limited the treatment duration to 24 weeks with an adequate description of the limitations in terms of long-term efficacy data.

Tests of statistical significance included the paired, 2-tailed t test and the unpaired t test. Testing for statistical significance was only done for subjects who completed the study and with respect to mean treatment changes on mTDS. The statistical tests are sub-optimal in a cross-over trial, the standard test is ANOVA with factors: Sequence, subject, period, and treatment where subject to be nested in sequence. The Applicant has not managed to provide additional information allowing an ANOVA statistical testing, but this is justifiable since it is not critical for the benefit risk-balance. The lack of an ITT analysis with appropriate imputation technique could be a significant limitation to the interpretability of the study results depending on the number of subjects who did not complete the study. The Applicant clarified that the weekly assessments reflected an average impression of the drooling for the last seven days.

The scheduling of the IMP dosing without a standardised time window before and after intake of meal makes the rate and extent of absorption to study drug more variable. But GP administered with food would be expected to reduce the BA of GP and bias the study towards the 'null hypothesis' i.e. no difference between GP and placebo in terms of efficacy and tolerability. For the purpose of demonstrating overall efficacy in the study by Mier et al, the matter about food intake is therefore less of an issue.

The Applicant has not been able to confirm that the trial was conducted according to GCP rules applicable at that time. The reporting of the results has limitations which are the usual ones inherent with a bibliographic application. It is highlighted that this publication mix study methods with study results which does not facilitate its interpretation.

**Efficacy data and additional analyses**

Main study Zeller 2012a

The treatment effects seen on mTDS (responder analysis with 56.1% placebo subtracted responders on GP and mean change placebo subtracted improvement of 3.23 on GP) were clinically relevant although a smallest clinically meaningful difference was not reported as a basis for the sample size estimate.

The study population, with around 15% previous GP use in both treatment arms, was representative for the patient population which should allow for a reasonable generalizability of the study results. The limited previous use of GP should not have biased the study results.

Uncertainties remain, with respect to baseline factors like age, gender, race and ethnicity. Furthermore, an analysis estimating the variation for the primary endpoint (e.g. a bootstrapped 95% confidence interval)

would have been informative. Another uncertainty pertains to the lack of separate outcome data for subgroups of young children, older children and adolescents, respectively. .

Main study Mier 2010

The treatment effects seen on mean mTDS (improvement with glycopyrrolate from 7.52 to a maximum mean score of 1.85; placebo from 7.44 to 6.33) were clinically relevant although, as for the Zeller 2012a study, a smallest clinically meaningful difference was not reported as a basis for the sample size estimate. However, there are significant caveats in terms of the statistical test method used, the small sample size, and that the efficacy analysis was only performed for subject who completed the trial (27 subjects out of 39 subjects randomised). As for the latter point, in its response the Applicant made a conservative simulated data analysis on all 39 randomised subjects with BOCF for the 12 subjects who discontinued the trial and were not included in the published analysis. This decreased the placebo-subtracted mean treatment effect from 4.56 (in the published per-protocol analysis) to 3.06 on mTDS. The latter numerical difference of 3.06 is reassuring although it is not known whether this difference is statistically significant.

The study population that completed the trial is not described in detail, and no account is given for the subjects who dropped out. This puts question marks as to whether the study population was representative for the patient population and complicates the generalizability of the study results. As for the Zeller 2012a study, the limited previous use of GP should not have biased the study results.

Also one-third of the subjects deteriorated after having been titrated to their maintenance dosing. The MAH clarified that sialorrhoea is a condition in which the severity waxes and wanes over time, even on a daily basis (Blasco, 2002). As well as variation in response to treatment due to fluctuations in disease severity, other factors may have played a part such as administration of glycopyrronium bromide (GP) with vs. without food, and the established intra-subject variability in bioavailability of GP, which may have been more significant in this study given the extemporaneous (pharmacy-prepared) capsules that were used.

Uncertainties with this study relates to the study population not supporting the treatment age as of three years in the proposed SmPC), but a treatment age as of four years. Other important uncertainties relate to the statistical test method used for the primary endpoint and the high percentage of subjects with early discontinuation (31%) combined with a statistical efficacy analysis only encompassing subjects who completed the trial.

The long-term study by Zeller et al, 2012b was an open label clinical trial without placebo control. The reported responder rate at week 24 was based on 130 subjects (out of 137 originally enrolled subjects) suggests a reasonable maintenance effect over a 24-weeks treatment period among subjects who responded however the efficacy results from this trial cannot be considered conclusive, but only indicative of long-term efficacy due to the limitations of the trial design. Based on the limited evidence on long term use the Applicant reduced the duration of use in the SmPC to 24 weeks to mirror the available efficacy data.

Supportive studies by Stern 1997, Blasco et al 1996 used different formulation of GP compared to the applicants preparation and were conducted in mixed paediatric-young adult population. The publications provide only limited methodological information and no comparative treatment/placebo were used. No conclusions with regards to efficacy can be drawn due the limitations of the trial design.

Also Arbouw et al 2010 used a different formulation of GP compared to the applicant's preparation. This trial demonstrates proof-of-concept for treatment of sialorrhoea in PD subjects and generally suggests proof-of-mechanism in the treatment of sialorrhoea. However no conclusions with regards to efficacy in paediatric subjects with sialorrhoea can be drawn due to the chosen study population.

There are no specific data presented with glycopyrronium to assess its effect on quality of life (QoL). The Applicant submitted data on a mapping exercise to estimate utility values for drooling in cerebral palsy (QoL Mapping).

There are several limitations in relation to this analysis. The sample size was small and relationships between utility and drooling and other Cerebral Palsy severity characteristics have not been considered. Also the mapping algorithm was developed based on a different population (healthy children attending secondary school), including a different age cohort (11 – 15 year olds, rather than 2 – 6 year olds included in the Chang et al., dataset), and based on self-report, rather than proxy report in the Chang et al., study.

From the analysis the difference in quality of life in paediatric patients with cerebral palsy is significant between patients who drool and those who never drool. This is further supported by the evident decreasing of quality of life linked to increasing severity of drooling. However, the analysis does not take into account for the possible very unpleasant adverse effects of Sialanar, which would affect the Quality of life during treatment.

### 2.5.4. Conclusions on the clinical efficacy

The two main studies for demonstrating clinical efficacy, which exposed less than 50 subjects to treatment with GP in the claimed indication, both met their primary and secondary efficacy endpoints. Taken together these studies only support a treatment age as of three years and the indication was adapted by the applicant accordingly. The Zeller 2012a study has some methodological limitations and the Meier study has considerable uncertainties. None of the studies support chronic use of GP in paediatric subjects with sialorrhoea from a clinical efficacy perspective. Nor does the Zeller 2012b study with a 24-weeks treatment, which was open label without placebo comparison. A maximum treatment duration of 24 weeks was proposed by the applicant which is more appropriate, considering the available efficacy data.

Both the main studies were performed with other formulations/preparations than the Applicant's product, and bioequivalence has not been established between these formulations/preparations. On the contrary, the Applicant's preparation (Sialanar) and tablets of GP (used in the Mier study to compound capsules) have a higher bioavailability than the product used in the Zeller 2012a study. Therefore the recommended initial dose and dose titration schedule has been revised taking into account the higher bioavailability of the Sialanar formulation. With the revision of the dose recommendations, it is reasonable to conclude that the efficacy results of the Zeller studies can be applied to Sialanar.

As reflected in the mapping exercise, the quality of life in children with pathological drooling due to cerebral palsy is clearly affected compared to children with cerebral palsy who do not drool.

This is not disputed; there is however a concern that any improvement would be offset by the presence of detrimental adverse effects associated with the treatment.

## *2.6. Clinical safety*

The safety data presented in support of this application in children with neurological disorders are derived from six published articles; Zeller 2012a, Zeller 2012b, Mier 2000, Blasco 1996, Stern 1997 and Bachrach 1998. The studies presented in the Zeller articles were the pivotal studies for the approved reference product (Cuvposa). Supportive articles of the use of GP in adults as well as the Applicants proof of market research, the Proveca report, and a MHRA DAP (Drug Analysis Print) has also been provided.

## Patient exposure

### Exposure in children

Patient exposure from the studies by Zeller et al studies are summarised below:

**Table 14 Exposure to Cuvposa (1mg/5ml); (Zeller, 2012a and Zeller, 2012b)**

| | Cuvposa (1 mg/5 ml) | | Placebo |
|---|---|---|---|
| | Zeller, 2012a N=19 | Zeller, 2012b N=137 | Zeller, 2012a N=18 |
| Mean total daily dose ≥0.1 mg/kg to ≤0.2 mg/kg | 68.4% | 51.1% | NS |
| Reached maximum GP dose level (0.1 mg/kg tid) | 52.6% | 7.3% | 82.3% |
| Duration of exposure | | | |
| Mean | 55.4 days | 139.8 days | NS |
| >50 to ≤ 100 days | 89.5% | NS | - |
| >150 to 200 days | - | 75.9% | - |
| Titration required (N or %) | | | |
| Up | 56 | - | 67 |
| Down | 11 | 45% | 3 |

Data source: Zeller, 2012a; Zeller, 2012b

NS = not specified; tid = three times daily

Patient exposure from the studies by Mier, Blasco, Stern and Bachrach are presented below:

**Table 15 Exposure to glycopyrronium bromide across all studies of glycopyrronium bromide for sialorrhoea in paediatric population**

| | Mier, 2000 | Blasco, 1996 | Stern, 1997 | Bachrach, 1998 |
|---|---|---|---|---|
| Number subjects | 27 | 38 [a] | 22 | 37 |
| Mean dose (mg/kg/day) | - | 0.01-0.82 [b] (median 0.09) | 0.04-0.1 (maximum 0.175) | 0.051 |
| Mean length exposure | 4-week dose titration + 4-week maximum dose period | Up to 4 years | 5 weeks to 28 months | 20.3 months (no side-effects)<br>13.0 months (with side-effects) |
| Mean (range) highest tolerated dose | | - | - | - |
| mg | 2.49 (1.2 to 3.0) | - | - | - |
| mg/kg/dose | 0.11 (0.04 to 0.2) | - | - | - |

Data source: Mier, 2000; Blasco, 1996; Stern, 1997; Bachrach, 1998

a. An additional 2 subjects are excluded as responses could not be determined due to immediate allergic reactions to GP.

b. 0.82 mg/kg is believed to be a typographical error in the publication

**Exposure in referenced adult studies**

The study by Arbouw et al, 2010 was conducted in adult subjects (N=23; mean [SD] age: 70 ± 7.8 years), predominantly (19/23, 82.6%) of male gender with PD (mean [SD] duration: 10.2 ± 8.6 years), with a mean (SD) baseline sialorrhoea score, assessed using the mTDS, of 6.5 ± 1.3.

The comparative PK study, PRO/GLY/001, conducted by the Applicant was performed in adult healthy volunteers (N=66; mean [SD] age: 24.5 ± 6.6 years), predominantly (39/66, 59.1%) of male gender. The majority of subjects (80%) were black.

## *Adverse events*

When assessing the occurrence of adverse events it is important to know how the adverse events have been collected. The six studies, which provide the safety data on children with neurological disorders, all employed different methods of capturing the AEs.

*Oral solution: Zeller, 2012a and Zeller, 2012b*

A large part of the AE monitoring in the trials was conducted in conjunction with each subject's parent/caregiver (P/C). The P/C used a diary. The diary contained a specific checklist of anticholinergic associated AEs as well as other general signs associated with AEs. In particular, the diary included the 28 item modified Behavioural and Medical Rating Scale (mBMRS) (table below), which was developed by

Camp-Bruno et al, 1989. This scale was designed to uncover expected cholinergic affects as well as subtle AEs by probing for both signs and symptoms of AEs. The diary was completed 3-times-per week by P/C. The mBMRS, which was also used by investigators, aided in the identification of possible AE-related behaviours and physiological effects in individuals taking GP.

**Table 16 Adverse events listed in instruments used for capturing parental/caregiver reports studies by Zeller of glycopyrronium bromide for sialorrhoea**

| Zeller, 2012a; Zeller, 2012b | | Mier, 2000 |
|---|---|---|
| modified Behavioural and Medical Rating Scale[a] | | Drowsy |
| 1. Restless, overactive | 15. Constipation | Restless, overactive, or short attention span |
| 2. Excitable, impulsive | 16. Drowsy | Easily frustrated, irritable |
| 3. Disturbs others | 17. Nasal congestion | Rapid mood changes |
| 4. Fails to finish things, short attention span | 18. Vomiting | Temper outbursts, explosive behaviour |
| 5. Constantly fidgeting | 19. Irritable | Overly sensitive, serious, sad, cries easily |
| 6. Inattentive, easily distracted | 20. Dry mouth | Fearful |
| 7. Demands must be met immediately | 21. Difficulty urinating | Worsening coordination |
| 8. Cries often and easily | 22. Flushing of skin on face or body | Facial flushing |
| 9. Mood changes quickly and drastically | 23. Headache | Nasal congestion |
| 10. Temper outbursts | 24. Blurred vision | Excessively dry mouth |
| 11. Overly serious, sad or sensitive | 25. Heart palpitations | Vomiting |
| 12. Change in coordination | 26. Increased heart rate | Constipation |
| 13. Fearful | 27. Skin rash | Diarrhoea |
| 14. Diarrhoea | 28. Skin hives | Difficulty emptying bladder |

Data source: Zeller, 2012a; Zeller 2012b; Mier, 2000; Camp-Bruno, 1989

a. Each item on the scale was assessed using the following descriptors: 1 = not at all; 2 = just a bit; 3 = quite a bit; 4 = very much.

Safety was also evaluated with the following clinical testing:

1. Physical examination at Screening and Week 8 (Zeller, 2012a) or Week 24 (Zeller, 2012b);
2. 12-lead ECG at Screening and Week 8 (Zeller, 2012a) or Weeks 4, 12, and 24 (Zeller, 2012b);
3. Clinical laboratory evaluations (blood chemistry, haematology, and urinalysis) at Screening and Week 8 (Zeller, 2012a) or Week 24 (Zeller, 2012b); and
4. Vital sign measurements at Screening and during Weeks 1, 2, 4, 6, and 8 (Zeller, 2012a) or Weeks 1, 4, 8, 12, 16, 20, and 24 (Zeller, 2012b).

If a subject prematurely withdrew from the study before the last scheduled visit, safety assessments were performed at the time of discontinuation from the study.

Specific laboratory testing included:

1. Haematology: haemoglobin, haematocrit, red blood cell count (RBC), white blood cell count, differential WBC count, (i.e., neutrophils, basophils, eosinophils, lymphocytes, monocytes), platelets;
2. Serum biochemistry: creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, total bilirubin, calcium, phosphorus, uric acid, cholesterol, total protein, albumin;
3. Urinalysis: dipstick (leukocytes, protein, blood, glucose, ketones); if abnormal: microscopic sediment examination (erythrocytes, leukocytes, bacteria, casts, epithelial cells);
4. Thyroid stimulating hormone and free T4 (in nonverbal, non-mobile patients): to screen for hyperthyroidism which can exist undetected in nonverbal, non-mobile patients;
5. Urine or blood pregnancy test: (if applicable).

In the studies by Zeller *et al*, clinically significant events were defined in the protocol as follows:

"Hematology values, blood chemistry values, urine values, and seizure grades that worsen more than one toxicity grade from baseline will be considered clinically significant (e.g., Grade 0 at baseline worsens to Grade 2, or Grade 1 at baseline worsens to Grade 3.)".

Since this patient population has a relatively high prevalence of seizure disorder, the baseline seizure grade was established through each subject's history (given by their P/C) before the subject started the trial. Changes from baseline were analyzed at the end of the study.

In the Zeller 2012a article it is stated that all 20 (100%) patients treated with glycopyrrolate oral solution and 15 of 18 (83.3%) who received placebo had at least one treatment-emergent AE (TEAE), including 15 (75%) and seven (39%), respectively, who had TEAEs considered by the investigator to be related to treatment. Four patients (20%) in the glycopyrrolate oral solution group, but none in the placebo group, had at least one severe. The most frequent AEs are shown below:

**Table 17**

**Table 2** Treatment-emergent adverse reactions occurring in ≥15% of patients treated with glycopyrrolate oral solution (1 mg/5 mL) and a greater frequency than placebo

| | Glycopyrrolate oral solution (1 mg/5 mL) (n = 20) n (%) | Placebo (n = 18) n (%) |
|---|---|---|
| Dry mouth | 8 (40) | 2 (11) |
| Constipation | 6 (30) | 4 (22) |
| Vomiting | 6 (30) | 2 (11) |
| Nasal congestion | 6 (30) | 1 (5) |
| Flushing | 5 (25) | 3 (17) |
| Urinary retention | 3 (15) | 0 |

In the open-label study by Zeller *et al*, 2012b, 89% of subjects had at least one TEAE, most frequently constipation (20.4%). Most patients (n = 122; 89%) had at least one treatment- emergent adverse event, 47% of which were deemed related to oral GP, with most being mild-to-moderate in intensity. The most commonly reported treatment-emergent adverse events are summarised in the table below:

**Table 18 Most commonly reported treatment-emergent adverse events.**

| Adverse event | Oral GP solution 1 mg/5ml (Cuvposa) |
|---|---|
| Constipation | 28 (20.4%) |
| Vomiting | 24 (17.5%) |
| Diarrhea | 24 (17.5%) |
| Pyrexia | 20 (14.6%) |
| Dry mouth | 15 (10.9%) |
| Flushing | 15 (10.9%) |
| Nasal congestion | 15 (10.9%) |

Zeller, 2012b

Several treatment-emergent adverse events occurred more frequently in the high-dose (>0.2 mg/kg) and middle-dose (≥0.1 to ≤ 0.2 mg/kg) than in the low-dose (<0.1 mg/kg) group, including vomiting (18.4% versus 18.6% versus 13.8%), dry mouth (15.8% versus 11.4% versus 3.4%), otitis media (10.5% versus 10.0% versus 3.4%), upper respiratory tract infection (7.9% versus 10.0% versus 3.4, pneumonia (7.9% versus 5.7% versus 0%), streptococcal pharyngitis (7.9% versus 4.3% versus 3.4%), epistaxis (7.9%versus 4.3% versus 3.4%), somnolence (2.6% versus 8.6% versus 0%), pyrexia (18.4% versus 15.7% versus 6.9%), and rash (5.3% versus 11.4% versus 3.4%).

**Table 19 Adverse events by dose level in Zeller et al, 2012b**

| | Dose (mg/kg)[a] | | |
|---|---|---|---|
| **Event (%)** | **<0.1** | **≥ 0.1 – ≤ 0.2** | **> 0.2** |
| Vomiting | 13.8 | 18.6 | 18.4 |
| Dry mouth | 3.4 | 11.4 | 15.8 |
| Otitis media | 3.4 | 10.0 | 10.5 |
| URTI | 3.4 | 10.0 | 7.9 |
| Pneumonia | 0 | 5.7 | 7.9 |
| Streptococcal pharyngitis | 3.4 | 4.3 | 7.9 |
| Epistaxis | 3.4 | 4.3 | 7.9 |
| Somnolence | 0 | 8.6 | 2.6 |
| Pyrexia | 6.9 | 15.7 | 18.4 |
| Rash | 3.4 | 11.4 | 5.3 |

Data source: Zeller, 2012b

Note: the publication does not state if this is individual or daily dose. Given the range is above that of an individual dose, the Applicant believes these doses are daily doses.

It is clear that typical anticholinergic AEs occurred with a higher incidence in the GP arm than in the placebo arm in the Zeller 2012a article. This is in contrast to what was found in the placebo controlled study by Arbouw, 2010 in adults with Parkinson's disease (GP 1 mg of a 0.2 mg/mL admixture or placebo). In this study there were no significant differences in AEs between GP and placebo treatment. Although this is an indirect comparison, and as such be interpreted with caution, the AE profile of GP in adults cannot readily be extrapolated to children. This thus supports the importance of sufficient placebo controlled safety data in children. There is no information in the Zeller 2012a article on dose dependent AEs which would have been valuable information. There is only information on how many had a dose increase (56 up-titrations) and decrease (11 down-titrations). Additionally, there is no information on the incidence of AE per age group.

The open-label Zeller 2012b (n=137) study confirms that typical anticholinergic AEs were seen. 89% of the patient had an AE, 47% of which were deemed related to GP. Additionally, the information on dose dependent AEs show that a higher dose is associated with a higher incidence of AE. However, as this was an open label study the exact incidence of an AE at a certain dose level should be interpreted with caution.

Crushed encapsulated Robinul tablets: Mier, 2000:
P/C were questioned each week by telephone regarding the presence of any of 15 pre-specified AEs (see table further above *Adverse events listed in instruments used for capturing parental/caregiver reports in pivotal studies of glycopyrronium bromide for sialorrhoea*) as well as the presence of any other events that were not on the list. A physical examination was performed at each visit, with particular attention paid to the presence of erythema, maceration or induration around the mouth, weight, and blood pressure.

25 (69%) of 36 subjects reported AEs associated with the use of GP orally, compared with 5 (17%) of 30 during the placebo phase.

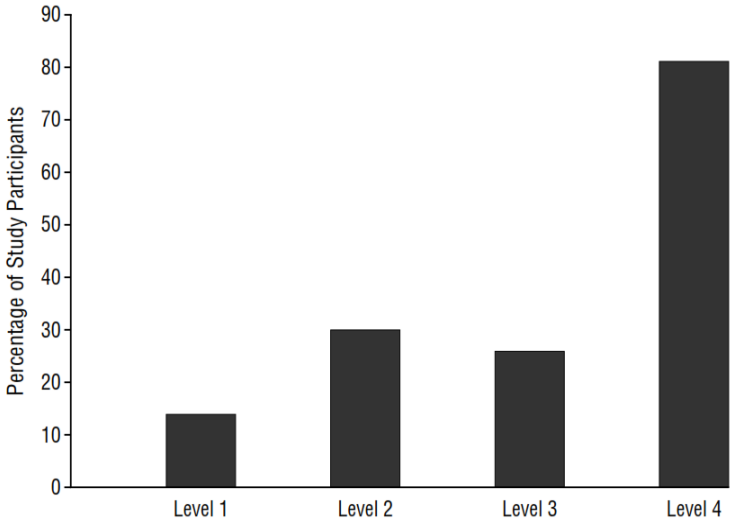
**Table 20 Frequently reported adverse events in Mier 2000**

| AE term | Crushed encapsulated Robinul tablets N=36 (%) | Placebo N=30 (%) |
|---|---|---|
| Behavioural changes[a] | 23 | 3 |
| Constipation | 18 | 0 |
| Excessive dryness or mouth or secretions | 18 | 0 |
| Urinary retention | 13 | 0 |
| Facial flushing | 10 | 0 |
| Nasal congestion | 10 | 3 |
| Vomiting | 10 | 0 |
| Diarrhoea | 10 | 3 |

Data source: Mier, 2000

a Includes drowsiness, restlessness, overactivity, short attention span, frustration, irritability, mood changes, temper outbursts, explosive behaviour, excessive sensitivity, seriousness, sadness, frequent crying episodes, fearfulness

**Proportion of subjects experiencing AEs by dose level**




| Baseline weight | Dose level: | Glycopyrronium bromide tablet dose mg (mg/kg) | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 |
| <30 kg | | 0.6 (>0.02) | 1.2 (>0.04) | 1.8 (>0.06) | 2.4 (>0.08) |
| >30 kg | | 1.2 (<0.04) | 1.6 (<0.06) | 2.4 (<0.08) | 3.0 (<0.1) |

Data source: Mier, 2000

The Mier, 2000 article mentions that younger children tended to exhibit adverse effects more often than older children and that, the difference did not achieve statistical significance.

The Mier, 2000 study differs from the Zeller, 2012a study on several key points and is not considered to be a pivotal safety study. Furthermore, from the limited information provided on the collection of AEs it is evident that this was performed differently than in the Zeller study. However, 25 (69%) children had an AE while taking GP versus 5 (17%) taking placebo. Many had the same frequent AEs as described in the Zeller articles, though behavioural changes was seen in 23% of the children in the Mier trial. Behavioural change was not described as an AE occurring with a frequency of more than 15% in the Zeller 2012a article. Somnolence is the only AE in the Zeller 2012b article which can be categorised as a behavioural change. It occurred with a frequency of 8.6% in the middle dose and 2.6% in the high dose category. The Blasco, et al 1996, article reported of behavioural changes in 13% of the children. These differences in frequency of AEs, which could be categorized as behavioural changes, are surprising.

The placebo-controlled study by Mier, 2000 seems to confirm that the AEs are more frequently seen with high doses (more than 0.08 mg/kg/dose). This level corresponds to the Applicant's proposed dose level 4 and 5.

*Stern et al 1997, open label study*

The AEs reported the Stern et al 1997 (n=24), open label study should be interpreted with caution, as the information provided in the article is not sufficient to assess if the capture of the AEs was done satisfactorily.

It is mentioned that "*They were asked to report possible side-effects or any concerns they had. Close contact was maintained with all the participants. Duration of therapy varied from 5 weeks to 28 months. Sometime after the end of the trial parents were asked to complete a questionnaire in order to assess the effect of glycopyrrolate*." Only the caregiver/parent assessed AEs, and it not known when the AEs were reported. This could lead to a risk of significant underreporting. This insufficient way of capturing AEs is most likely reflected in the recorded AEs which were: thirst in hot weather in two children, dilated pupils in one child, one report of flushed face, constipation in two children, bad breath in one child and dry lips in one child.

*Blasco 1996, open label study*

**Table 21 Adverse events reported in Blasco 1996**

| AE term | Glycopyrronium bromide N=40 n (%) |
|---|---|
| Any AE | 13 (32.5) |
| Irritability[a] | 5 (12.5) |
| Constipation | 3 (7.5) |
| Hives | 2 (5.0) |
| Urinary retention | 1 (2.5) |
| Dry mouth[b] | 1 (2.5) |
| Epistaxis[b] | 1 (2.5) |
| Skin flushing[a] | 1 (2.5) |
| Headache | 1 (2.5) |

Data source: Blasco, 1996

One patient had AEs of irritability and skin flushing

All patients were prescribed glycopyrrolate, starting at a dose of 0.5 mg once or twice daily. It is stated that "*Patient responses and side effects were initially monitored by telephone every 5 to 10 days to establish the effective dose clinically and to monitor for benefits and side effects*". Follow-up ranged from 8 months to 4 years. This means that only the patient and/or presumably the caregiver/parent assessed AEs. Additionally, it is mentioned that there was a regular *initial monitoring*. It is not stated how long the monitoring period was. This way of capturing AES could explain the differences in the incidence of reported AEs compared to the Zeller (and Mier) article. Surprisingly, 68% did not experience any AEs. Those that did experience an AE experienced the same type of AEs as in the Zeller studies except for irritability.

*Bachrach 1998, retrospective survey*

17/37 (46%) GP-treated patients experienced AEs. The most commonly reported events were dry mouth and/or thick secretions in 7/37 (18.9%), urinary retention in 7/37 (18.9%), flushing in 4/37 (10.8%), constipation in 2/37 (5.4%), pseudo-obstruction in 1/37 (2.7%), and agitation and personality change in 1/37 (2.7%).

54 patients were identified for whom antisialorrheic medication had been prescribed for treatment of either excessive drooling or tracheal secretions. Questionnaires were mailed to these families. A total of 41 questionnaires were completed (76%). The questionnaire asked for parents or caretakers to indicate whether their child was still taking medication for drooling, what the medication was, and whether they had experienced any side effects from medication. Potential anticholinergic side effects were described to the parents before the medication was started. 37 of 41 were treated with GP. Seventeen of 37 (46%) reported that their children experience adverse events while taking glycopyrrolate. The most frequently reported adverse event were AEs also frequently reported in the Zeller study. It is mentioned that there was no difference in the dose between those who experienced an AE and those who did not. However, it not known when the child experienced the AE and given the design of the study there is a high risk of underreporting.

**Analysis of Adverse Events by Organ System or Syndrome**

*GI system:* GI comorbidity is common in individuals with CP. Thus, primarily placebo controlled trials can be used to ascertain if GP causes GI adverse effects.

It is evident from the two placebo-controlled studies, Zeller, 2012a and Mier, 2000 that GI AEs occurred more frequently in children treated with GP than with placebo. The Zeller, 2012a article; constipation (30% vs. 22%) and vomiting (30% vs. 11%). Mier, 2000 article; constipation (18% vs. 0%), vomiting (10%. vs. 0%) and diarrhea (10% vs. 3%).

*Renal function and urogenital system*: Regarding urinary retention, the two placebo controlled studies, Zeller 2012a and Mier 2000 report that 13-15% patients had urinary retention while treated with GP vs. 0% when treated with placebo. There is no information on the severity of the urinary retention or if it was associated with an increased incidence of urinary tract infections. Additionally, as GP is intended as chronic treatment there could be a risk of chronic urinary retention leading damage to the bladder by overextension. Additionally, there is a risk of reflux leading to tubular atrophy and, eventually, irreversible renal injury.

*Cardiovascular system including ECG:* GP, as an anticholinergic, is expected to result in hear rate (HR) increase. There is no information on how much HR increases with GP treatment in children with neurological disorders.

The only article to mention ECG results is Zeller, 2012b. It is stated that there was no abnormal or clinically significant shifts in ECG findings in subject who had had an ECG at baseline and at week 24. The number of patients with baseline and week 24 ECG recordings is not stated. Additionally, there are insufficient details regarding the ECG result allow an independent review. Furthermore, as the tachycardic effects are dose-related and because of the fact that the Applicant oral solution of GP, GBOS, is 25% more bioavailable, the ECG results obtained from the Zeller study, where Cuvposa was used, cannot readably be extrapolated. However, the plasma concentrations in the PRO/GLY/001 study, conducted in healthy adults with a mean dose of 0.03 mg /kg, was comparable to the plasma concentrations in the QT interval study by Drollman et al, 2014. This study investigated QT prolongation properties of inhaled GP in adults and found that the GP doses tested did not cause QT prolongation. Sialanar simulated plasma concentration (Cmax) is around 962 pg/ml (median=941 pg/ml) in 3 year old children, i.e. the youngest included in the indication and thus selected for simulation as representative of the worst case scenario. The upper limit of the 95% confidence interval is of around 2000 pg/ml. This is comparable to the plasma concentrations in the QT interval study by Drollman et al, 2014.

*CNS:* The highly polar quaternary ammonium group of GP limits its passage across lipid membranes, such as the blood brain barrier (BBB). In adults, GP does not seem to cross the blood brain barrier (BBB). However, in a study in children with hydrocephalus, GP was detected in the CSF. This suggests that GP might pass the

BBB. Additionally, non-clinical data suggest that GP could cross the BBB in some species (please refer to non-clinical AR). The articles by Zeller do not mention frequent CNS AEs. However in the Mier, 2000 article, 23% treated with GP vs. 3% treated with placebo had behavioural changes. It is not known if GP affects neurodevelopment.

*Oral mucosa and teeth*: Decreased salivation may also increase the risk of developing oral diseases and make patients susceptible to mucositis, especially candidiasis. A possible consequence of reduced salivary flow is an increased risk of dental caries. In particular in subjects with more advanced neurological disorders, development of caries would be a major concern since this group of patients often need dental treatment under general anaesthesia. The increased risk of dental caries has been added as a warning to the SmPC.

## Serious adverse event / deaths / other significant events

### Serious Adverse Events

SAEs were reported in both Zeller studies and also in the Applicant's comparative PK study (PRO/GLY/001). No information regarding SAEs are available in the other studies of GP in children with neurological disorders. The SAE in the PK study with adults was tonsillitis and is not considered treatment related.

In Zeller *et al* 2012a, one patient (5.0%) in the GP group experienced a serious AE, generalised tonic-clonic seizure activity followed by generalised convulsions, 8 days after the last dose of study drug, which was not considered related to study drug; no placebo patient had a serious AE. In Zeller *et al* 2012b, fourteen patients (10%) had 20 serious adverse events, 8 while taking the study drug and 6 within 30 days of the last dose. Of these 20 serious adverse events, four were considered treatment-related, ie, nystagmus, oesophageal candidiasis, dehydration and gastrointestinal motility disorder.

The higher incidence of SAE (10 % in Zeller, 2012b vs. 5% in Zeller 2012a) is not surprising as the Zeller 2012b study was a 24-week study, and the Zeller 2012a study was only an 8-week study. It is not mentioned if the serious AEs resolved, in what age group and at what dose level they occurred. It is noteworthy that in the adult study presented in the article by Arbouw, 2010, there were no SAEs. This is of course an indirect comparison and should be interpreted with caution, but seems to suggest that incidence the severity/seriousness of AEs in adults when treated with GP cannot readily be extrapolated to children with neurological disorders.

### Deaths

There were no reported deaths in any of the pivotal or supportive studies, other than the 24-week open-label study by Zeller *et al*, 2012b. Three subjects died within 30 days of the last dose of study drug due to SAEs, one each due to multisystem organ failure, anoxic encephalopathy, and aspiration pneumonia, but none was considered treatment related by the investigators; no additional deaths occurred after 6 months follow-up.

**Table 22 Summary of deaths in Zeller 2012b**

| No. of Subjects | Preferred term | Severity | Outcome | Relationship |
|---|---|---|---|---|
| **Glycopyrrolate oral solution (1 mg/5 ml), N=137 (Zeller, 2012b)** | | | | |
| 1 | Multi-organ failure | Severe | Death | Not related |
| 1 | Pneumonia aspiration | Severe | Death | Not related |
| 1 | Anoxic encephalopathy | Severe | Death | Not related |

Data source: Zeller, 2012b

Even if the article mentions that the three deaths were not related to the treatment, only limited information is provided. Thus, it is not possible to provide an independent assessment of a causal relationship between the deaths and GP treatment. However, the Applicant has provided published literature to support that the number of deaths in the Zeller 2012b article does not exceed the expected number of death in this patient population. Additionally, the deaths did not occur while the patients were treated with GP.

***Oral solution: Zeller, 2012a and Zeller 2012b***

In Zeller *et al* 2012a one patient (5.0%) in the GP group experienced a serious AE, generalized tonic-clonic seizure activity followed by generalized convulsions, 8 days after the last dose of study drug, which was not considered related to study drug; no placebo patient had a serious AE. In Zeller *et al* 2012b, fourteen patients (10%) had 20 serious adverse events, 8 while taking the study drug and 6 within 30 days of the last dose. Of these 20 serious adverse events, four were considered treatment-related, ie, nystagmus, oesophageal candidiasis, dehydration and gastrointestinal motility disorder.

## Laboratory findings

There are only laboratory results available from the Zeller 2012b article.

Haematology: There was an increase in monocytes in approximately 15-10% of the patients. There was a decrease in neutrophil count (11% of the patients) and red blood cell count (11% of the patients). There is no additional information regarding the degree of changes in the haematological parameters, whether it was only a transient change and if there were other possible explanations for the changes, such as infection etc.

Serum chemistry: There is no information on the extent of the decreases in bicarbonate, carbon dioxide and creatinine. There can be several reasons for the observed decrease and it is not known if these are clinically relevant. These changes have not been reported as adverse events when glycopyrronium has been used in adults in other formulations.

## Vital Signs, Physical Findings, and Other Observations Related to Safety

Only the Zeller 2012b article refers to vital signs etc. In the article, it is stated: *Although there were minor fluctuations in vital signs, including mean systolic and diastolic blood pressure, pulse rate, respiration rate, temperature, and weight, over the course of the study, none of these changes was clinically notable.*

Considering that treatment is meant for children, it is important to know if there are any adverse effects on development including weight, height and neurodevelopment, especially considering that this is a chronic treatment. Neurodevelopment may be difficult to assess in a population of patients with neurological

disorders. However, weight and height can be monitored. Growth is not even mentioned in the Zeller article, so it is impossible to assess any potential effect on growth. Additionally, none of the studies with duration of more than 12 months mention growth or weight.

The Applicant has proposed to reduce the duration of treatment to 24 weeks. This could in theory reduce the likelihood of an adverse effect on neurological development and growth. However, even 24 weeks of treatment could result in an adverse effect on e.g. neurodevelopment, and repeated courses of treatment are not unlikely in a clinical setting.

## Safety in special populations

Safety results with regard to different age groups within the patient population suggest that younger patients experience a higher incidence of adverse events, though there is limited data.

Safety results in other special populations, such as populations defined by gender, race, renal function and hepatic function have not been presented. However, adult studies using other formulation of glycopyrronium as well as the PK study conducted with Sialanar does not suggest that gender or race affects the risk of adverse event. Additionally, an acceptable dose reduction in patients with mild to moderate renal impairment has been included in the product information (see also chapter on pharmacokinetic of this assessment report.

### Intrinsic Factors

No information is available in the public domain on the interaction between demographic factors and safety of GP.

### Safety in paediatric patients

The Applicant has developed GBOS (0.4 mg/mL) specifically for the treatment of sialorrhoea in children with neurological disorders. The proposed posology is based upon patients weight (and thus, indirectly, age). Although younger subjects tended to exhibit AEs more often than older subjects in the study by Mier *et al*, 2000, this difference was not statistically significant. The mean age of subjects who discontinued treatment due to AEs was 8 years 7 months, whereas the mean age of subjects who completed the study was 10 years 11 months, (p=0.015). An assessment of impact of age upon AE rates was not reported in the studies by Zeller *et al*.

### Use in Pregnancy and Lactation

No human reproduction studies have been performed. However radiolabelled GP was administered to patients undergoing a Caesarian section in a study by Ali-Melkkilä *et al*, 1990b. In that study, low, clinically insignificant, levels of GP were detected in the umbilical venous (0.28 ± 0.25 ng/mL) and in the umbilical arterial (0.18 ± 0.11 ng/mL) plasma 86 minutes after administration of a 6 µg/kg i.m. dose. In another study GP 4.4 µg/kg given i.v in 20 term partuants had no effect on foetal heart rate or heart rate variability, whereas an increase in maternal heart rate was noted (Abboud, 1981). A foetal antisialogogue effect cannot be ruled out, however the MHRA DAP for glycopyrrolate (period 01-Jul-1963 to 15-Apr-2014) does not contain any reports of AEs relating to reproduction or pregnancy (MHRA, 2014b).

It is not known if GP is excreted in breast milk, although its highly ionized state makes this unlikely (Dollery, 1998).

### Extrinsic Factors

### Climate

As discussed previously, GP can have an effect on temperature homeostasis, which may be exacerbated in hot climates. However, no specific labelling is considered necessary.

**Renal and hepatic impairment**

The Applicant notes that congenital hepatic abnormalities are very rare in patients with non-acquired CP (Rankin, 2010). The effects of hepatic impairment on the PK of GP have not been investigated. Since the predominant route of elimination of GP is renal, a clinically significant change in GP exposure due to hepatic impairment is not expected, and therefore a difference in AE profile in this population is considered to be unlikely.

GP is renally eliminated, and renal abnormalities and thus presumably renal impairment occur in children with cerebral palsy. It is thus important to know if adverse event occur more frequently and/ or are more severe in patients with renal impairment. The Applicant proposed to contraindicate the use of GP in patients with severe renal impairment based on a significantly higher exposure in patients with severe renal impairment. This is accepted.

A moderate mean increase in total systemic exposure (AUClast) of up to 1.4 fold was seen in adult subjects with mild and moderate renal impairment [estimated GFR greater than or equal to 30 mL/min/1.73m2] and up to 2.2 fold in subjects with severe renal impairment end stage renal disease [estimated GFR less than 30 mL/min/1.73m2] (Sechaud et al., 2102a). Based on extrapolation of results from adult subjects with mild to moderate renal impairment, the Applicant proposes a dose reduction of 30% in children with mild or moderate renal impairment. Since Sialanar will be titrated based on an assessment of efficacy and side effects, the proposal was included into the SmPC. Given the very limited data, also a warning regarding mild and moderate renal impairment in the SmPC was added. As GP elimination of GP is largely renal and impaired in patients with severe renal impairment, irrespective of the cause the applicant proposed a contraindication for these patients to which the CHMP agreed (please refer also to discussion on clinical pharmacology of this report).

## Safety related to drug-drug interactions and other interactions

**Food**

The Applicant has not conducted studies to assess the effect of food on the absorption of GP following administration of the proposed product, GBOS 0.4mg/5 mL. A high-fat meal significantly decreased the absorption of a single dose of glycopyrrolate oral solution 2mg in healthy adults. When administered under fed conditions, the mean Cmax and AUC∞ were both decreased by ≈75% compared with fasting conditions; median and mean tmax were not significantly altered. Glycopyrrolate should therefore be administered ≥ 1 hour before or ≥2 hours after meals (Garnock-Jones 2012).

Therefore, the Applicant proposed that dosing of GBOS occurs outside a time window around meals, by means of the following wording in the Posology section of the product labelling:

*Dosing should be at least one hour before or two hours after meals.*

Many children with CP and other neurological disorders require feeding via a tube, thus the Applicant's product is likely to be administered via a feeding tube in many cases. Given the narrow therapeutic margin of GP this has implications for the safe use of the product. The compatibility of the product with administration via a feeding tube was assessed in Measure 1 in the Applicant's Paediatric Investigational Plan (PIP), through Protocol CF014-003 (Feeding Tube Study). The aim of this study was to determine the volume of water flushing required in order to clear the feeding tubes of residual product (>99% dose

recovery) following administration of the Applicant's GBOS 2 mg/5 ml. A minimum volume of 0.5 ml and a maximum volume of 7.5 ml of GBOS were tested across a range of feeding tubes. This volume/dose range is equivalent to the lowest initial dose for a child weighing 10-15 kg (minimum dose) and the highest maximum tolerable dose for a child weighing >26 kg respectively in the proposed posology. All feeding tubes assessed as part of this study showed complete clearance of the administered dose of GBOS 0.4 mg/mL after the first 10 mL of flush.

The recommendation to dose without food likely leads to less PK variability compared to having no recommendations or a recommendation to take with food. It is considered to reflects best the clinical data obtained with the formulation used in the Zeller studies. Deviations from the recommendation (i.e. taking Sialanar with food) would likely lead to increased PK variability and reduce glycopyrronium exposure. Despite fact that no food-drug interaction study has been performed with the GBOS formulation, the omission is considered acceptable given the above considerations.

**Drug interactions**

The SmPC has been updated to state that concomitant use of Sialanar and potassium chloride solid oral doses, topiramate, anticholinergic drugs or antispasmodic drugs should be avoided. Additionally, caution is advised with concomitant use of Sialanar and sedating antihistamines, neuroleptics/antipsychotics, skeletal muscle relaxants, tricyclic antidepressants, MAOIs, disopyramide, amantadine, nefopam, opioids, digoxin, corticosteroids, nitrates, beta-blockers, levodopa or neostigmine. Please also refer to the clinical pharmacology section.

## Discontinuation due to adverse events

Zeller, 2012a: One patient (5%) in the GP and one in the placebo group discontinued due to AE.

Zeller, 2012b: 10% discontinued due to a treatment related adverse event. The type of AE, age of the child and the doses used are unknown.

Mier, 2000: 18% withdrew due to an AE while treated with GP. The AEs leading to discontinuation were typical AEs associated with anticholinergic although behavioral changes were also mentioned. Of the seven children who discontinued, four did so before the end of the first week, while they were still receiving the lowest dosage level, a mean of 0.04 mg/kg/dose. The other three children discontinued at 10, 28, and 42 days, respectively while receiving a mean dose of 0.06 mg/kg/dose.

Blasco *et al*, 1996: 22.5% discontinued due to AEs. The AEs leading to discontinuation were similar to those mentioned in the Mier, 2000 article. There is no information about age and dose.

Bachrach *et al*, 1998, 27% discontinued due to AE anywhere from 1 to 20 months. It is furthermore stated in the article that "*Of the 11 patients who discontinued glycopyrrolate, three stopped it very quickly (within 2 months of starting the medication), whereas eight stopped it a year or more after beginning treatment. This would seem to indicate that long-term follow-up (of at least 1 year) is essential for an outcome study of treatment for drooling. In some of these patients the dose of medication was pushed higher because of lack of effect on the drooling, and this then caused side effects that necessitated discontinuing the medication*". The dose of those who discontinued was 0.053 mg/kg/dose and was similar to those who continued treatment. Two (5.4%) of the patient who discontinued due to AEs were younger than 2 years. No other information is available regarding age and the AEs leading to discontinuation.

In conclusion, 5-27% discontinued due to an AE. In the two articles reporting the highest discontinuation rate due to AE, Blasco et al, 1996 and the Bachrach et al, 1998, the titration scheme, including the increments of

the GP dose, was not reported. In the Mier, 2000 article, four (11%) patients withdrew in the first week with lowest starting dose (mean dose 0.04 mg/kg/dose). This is twice the recommended starting dose used in the Zeller studies and the dose proposed by the Applicant. The lower starting dose in the Zeller studies could possibly explain the lower discontinuation rate due to AEs in these studies. This could support the importance of choosing a low starting dose and only make small increments in the dose when titrating to the smallest effective dose. The two Zeller articles only offer limited information regarding the type of AEs, age of the child and the doses used for those who discontinued.

### Post marketing experience

At time of the submission this substance was not authorised in this indication. Therefore, there are no post-marketing data available.

## 2.6.1. Discussion on clinical safety

Whilst GP has been used for several decades, it has primarily been used in adults, in both acute and chronic settings and in formulations different from the oral formulation proposed by the Applicant. The AE profile established in other populations cannot readily be applied to a patient population of children with neurological disorders, which often have considerable comorbidity.

The safety data presented in support of this application in children with neurological disorders are derived from 6 published articles; Zeller 2012a, Zeller 2012b, Mier 2000, Blasco 1996, Stern 1997 and Bachrach 1998. The studies presented in the Zeller articles are, in terms of safety, the pivotal studies for this application. The supportive articles of GP in adults as well as the Applicants proof of market research, the Proveca report as well as the MHRA DAP (Drug Analysis Print) are of little value to conclude on the safety in the claimed indication.

The applicant informed if its intent to provide an oral dosing syringe with an 8 mL measure to accommodate the maximum single dose (6 mL). However, the CHMP questions the need for an 8 mL syringe as it may lead to an unintentional overdose.

The most critical shortcoming for this product which is intended to be used long term / chronically from a safety point of view is that the safety and tolerability profile in the indication is not appropriately characterized.

The overall size/quantity of the provided safety data is considered small and few patients have been exposed in the submitted publications of controlled trials as well as in long-term studies but most importantly the information provided are not sufficiently documented. There are not enough details on AEs, and for the studies Blasco 1996, Stern 1997 and Bachrach 1998, which provide the long term safety data the information provided in the articles is not sufficient to assess if the capture of the AEs was done satisfactorily.

Only the Zeller, 2012a article describes how many patients were included in the age groups 3-11 (n=12) and 11-18 (n=7). The development of the children in these categories differs, and thus it is important that the safety profile in a sufficient number of patients in each of these age groups can be assessed as the AE profile may differ.

In addition, for the age group 3-11 it is not known how many younger patients were included to ensure adequate representation across the age range in this category. This information cannot be retrieved from any of the presented articles. Hence, it is not clear if there is a sufficient number of children exposed in each of the age groups, and for the age group 3-11 in it not clear if a sufficient number of younger children have

been exposed to GP. Due to this lack of information, the incidence and severity of AEs by age group, and if patients in a certain age group had a higher discontinuation rate and at what dose level patients discontinued, cannot be ascertained.

Only the Zeller 2012a (n=38, 20 patients exposed to GP) article offers safety data from a placebo-controlled study where the posology resembles the posology proposed by the Applicant with regards to formulation used, initial dose, increments in dose during titration of the dose and recommendations with regards to administration with or without food. Oral formulations of GP presumably all have a significant food–drug interaction. The other article with placebo-controlled data, Mier 2000 (RCT cross-over study; n=39, 36 received GP) differs significantly with regards to posology. Thus, only safety data presented in the Zeller 2012a article can be considered pivotal placebo-controlled safety data. No other data where GP has been compared to placebo or active treatment in children have been presented which makes a detailed presentation of the safety profile in the remaining articles even more critical also because capturing and identifying AEs in children with neurological disorders can be difficult.

As the proposed treatment is a long-term treatment with chronic exposure, sufficient long-term (6 and 12 months or longer) safety data are required. The open-label Zeller, 2012b (n=137) study period was 24 weeks, thus less than 6 months. Only the two open-label studies, Blasco, 1996 (n=38; follow-up 8 months-4 years) and Stern, 1997 (n=22; duration 5 weeks to 28 moths), as well as the retrospective study Bachrach, 1998 (n=37; duration not clear though in the range of less than 2 months to more than 20 months), include long-term data (12 months or more). However, important details are missing from these articles regarding exposure. It is not known how many patients were treated for 6 and 12 months or more, how many patients older than 18 years were included, how many patients were in the age groups 2-11 years and 11-18 years and how many of these were exposed long-term. Furthermore, it is not known how many patients were treated with which dosages long-term, what formulation of GP was used (tablets, oral solution, grounded tablets), what dosing schedule was used, how titration was done and if there was any specific instruction given concerning the administration with or without food.

As already mentioned above also the quality of how the AEs were captured is questioned. In the Stern article, not enough information was provided on how the AEs were captured. It is only mentioned that "*They were asked to report possible side-effects or any concerns they had. Close contact was maintained with all the participants. Duration of therapy varied from 5 weeks to 28 months. Some time after the end of the trial parents were asked to complete a questionnaire in order to assess the effect of glycopyrrolate*". Only the caregiver/parent assessed AEs and it is not known when the AEs were reported. This insufficient way of capturing AEs is most likely reflected in the recorded AEs which were: thirst in hot weather in two children, dilated pupils in one child, one report of flushed face, constipation in two children, bad breath in one child and dry lips in one child . In the Blasco article it is mentioned that there was a regular *initial monitoring*. It is not mentioned how long the monitoring period was. AEs were only assessed by parents/caregivers.

This way of capturing AES could explain the differences in the incidence of reported AEs (68% did not experience any AEs) compared to the Zeller (and Mier) article. In the retrospective study by Bachrach, questionnaires were sent to parents/caregivers of children treated with GP at some point. Again, only the parent/caregiver assessed any AEs, and there is a risk of significant underreporting.

These concerns with regard to the quality of the methodology for capturing AEs and missing details on exposure of the long-term safety means that the information on AEs observed in the long-term studies should be interpreted with extreme caution.

Additionally, important information is lacking in the Zeller, 2012b article. There is also no information on how many children belonged to the age groups ≥ 3 to ≤ 11 and ≥ 12 to ≤ 18 years. The details provided on the deaths and serious adverse events are insufficient, and for the 10% who discontinued due to adverse events, the type of AE, age of the child and the doses used are unknown.

In the studies with the best and most thorough way of capturing AEs, the Zeller studies and the Mier study, 69-100% of the children had an AE. The placebo-controlled trials, Zeller 2012a and Mier 2000, report of an incidence of AEs for patients treated with placebo of 89% and 17%, respectively. The observed AEs were typical AEs associated with anticholinergics, such as constipation, vomiting, diarrhoea, urinary retention and flushing. Of these adverse events, urinary tract dysfunction including retention are frequent symptoms associated with cerebral palsy. However, urinary retention was not observed in the placebo group in either of the placebo controlled studies but occurred in 13-15% of the patients treated with GP. The high frequency of urinary retention with GP constitutes a major concern.

Pneumonia occurs often in patients with cerebral palsy and was also a frequent adverse event in the Zeller 2012b study and increased with increasing dose, which suggests a causal relationship to GP.

Across all studies 5-27% discontinued due to an AE. In the two articles reporting the highest discontinuation rate due to AE, Blasco et al, 1996 and the Bachrach et al, 1998, information was not provided on the titration schedule, including the dose increments. In the Mier, 2000 trial, four (11%) patients withdrew in the first week with the lowest starting dose (mean dose 0.04 mg/kg/dose). This is twice the recommended starting dose used in the Zeller studies and the dose proposed by the Applicant. The lower starting dose in the Zeller studies could possibly explain the lower discontinuation rate due to AEs. This could support the importance of choosing a low starting dose and only make small increments in dose when titrating to the lowest effective dose. The two Zeller articles only offer limited information regarding the type of AEs, age of the child and the doses used for those who discontinued. This is concerning as the design of these studies are the only studies who resemble the proposed posology by the Applicant.

Adverse events seem to be dose dependent, and the need for careful titration of the dose is confirmed by the Zeller articles where 56 up-titrations and 11 down-titrations were made in the Zeller 2012a study and 45% had a dose reduction in the Zeller 2012b study. An overall maximum tolerated dose cannot be estimated for GP. The maximum tolerated dose is subject to great inter-individual variation as illustrated in the Mier et al article, where the range of maximum tolerated dose was 0.04 mg/kg to 0.2 mg/kg.

Worryingly, considering the claim that GP does not cross the blood brain barrier, the Mier article reports that 23% of the children treated with GP had behavioural changes. The Blasco article mentions that 13% had behavioural changes while none of the other article mentions this AE as a frequent AE. This is not sufficiently addressed because a study in children with hydrocephalus showed that in some children GP crosses the blood brain barrier. Drowsiness, confusion, somnolence have been reported as adverse effects of GP. Since the patients with CP may suffer from fluctuating daily living capacity or may also suffer from various mental disorders, these neurological adverse effects are likely to be completely unrecognized or under-reported in the clinical studies. Decrease of daily activities/quality of life may be a negative consequence of these adverse events.

Considering that this is a chronic treatment meant for children, it is important to know if there are any adverse effects on development including weight, height and neurodevelopment. Neurodevelopment may be difficult to assess in a population of patients with neurological disorders. However, weight and height can be monitored. The Applicant mentions that no adverse effect on growth was reported. However, growth is not even mentioned in the Zeller articles, so it impossible to assess any potential effect on growth. Additionally,

none of the studies with a duration of more than 12 months mentions growth or weight. Even with the proposed reduced duration of treatment adverse effect on neurological development and growth may occur. Additionally, it is not unlikely that the child would receive more than one 24-week treatment courses. GP, as an anticholinergic, is expected to increase the heart rate (HR). There is no information in any of the articles on HR increases with GP treatment in children with neurological disorders. Additionally, there is insufficient information regarding effects on blood pressure. The only article mentioning ECG results is Zeller, 2012b, where it is stated that there was no abnormal or clinically significant shifts in ECG findings in subjects who had had an ECG at baseline and at week 24. However, the number of patients with baseline and week 24 ECG recordings is not stated. In addition, there is insufficient information regarding the ECG results to allow an independent review. Further, a thorough QTc study with an active (QTc prolonging) reference has not been conducted. However, extrapolation of the plasma concentrations in a QT study with inhaled GP suggests that the plasma concentration measured in study PRO/GLY/001 in healthy adults are similar and as such Sialanar does not cause QT prolongation at those plasma concentrations. Sialanar simulated plasma concentrations in 3 year old children are comparable to the plasma concentrations in the QT interval study with inhaled GP.

The Applicant provided data from the Clinical Practice Research Datalink (CPRD), an English NHS observational data and interventional research service.

Tabulations of undesired events by System Organ Class (SOC) and MedRA Preferred Term (PT) for the cohort of 428 children treated or likely treated for pathological drooling were presented. Events occurring throughout the child's life and during treatment plus the period shortly after treatment were tabulated separately. Some of the events are typical of a population of otherwise healthy children and adolescents, some typical of children or adolescents with neurological disabilities. It is acknowledged that some of the events that may be adverse effects of glycopyrronium also are seen in untreated patients.

The Applicant has also shown, based on the CPRD database, that a large proportion of the patients have been treated with glycopyrronium for more than 6 months and presented a tabulation of the most common adverse events for the cohort of 428 children treated or likely treated for pathological drooling by two age groups: < 12 years and 12-17 years.

A discussion for each of the areas of particular concern (heart rate and blood pressure, pneumonia and urinary retention) as well as other events (e.g. malignancies) was provided and the numbers of events in the cohort are generally low and the events are also seen when patients are not treated with glycopyrronium.

However, it is difficult to extract meaningful and pivotal information about the safety and tolerability profile of glycopyrronium from the CPRD database. Whilst this database provides valuable information, adverse events are not captured with the same rigor as in a randomised clinical trial or even an open-label clinical trial. This concern is supported by the fact that a number of events clearly identified as adverse effects of glycopyrronium from the randomised, placebo-controlled clinical trials, such as urinary retention (incidence on glycopyrronium about 13-15% vs. 0% on placebo), were reported with a substantially lower frequency in the database. It should be noted that these discrepancies are seen despite the fact that the average exposure per patient in the CPRD database was much higher than in the two placebo-controlled studies (Zeller, 2012a and Mier, 2000).

## 2.6.2. Conclusions on the clinical safety

In view of the uncertainties linked to the different posologies applied in the submitted literature, the overall size/quantity of the provided safety data, the quality of how AE were captured and insufficient details

provided on the patients exposed in controlled trials as well as in long-term studies, the clinical safety profile in children with neurological disorders is not adequately characterized

It is uncertain if the plasma concentrations of Sialanar in children and adolescents with neurological disorder could cause clinically relevant effects on blood pressure and heart rate. Hence, there is uncertainty about the cardiovascular safety of GP in this patient group. Urinary retention was reported with an incidence of 13-15% in the pivotal clinical studies whereas not occurring in the placebo arm and also pneumonia appears to be associated with GP use and there is insufficient information on the severity of these adverse events.

Also CNS effects have been reported with GP, and their significance in children with neurological disorders is associated with uncertainty. Additionally, there is no information on neurodevelopment or growth (height and weight) which may be affected particularly when treatment is applied chronically or in repeated episodes.

Furthermore it is unknown if the safety profile differs in different age groups. The provided data from a UK database (CPRD) are of observational nature, and adverse events from this database are unlikely to be captured with the same rigor as in a clinical trial. Hence, safety and tolerability data from this database cannot compensate for the deficient data package from clinical trials.

The Applicant proposed to limit the treatment duration to 24 weeks based on the data from the Zeller 2012b article. Reducing the duration of treatment could in theory reduce the risk of adverse developmental effects, but many patients will presumably be treated for several individual treatment episodes in view of the chronicity of the underlying conditions.

Furthermore uncertainties on the clinical importance of cardiovascular and CNS effects, urinary retention and the insufficiently characterized safety profile remain therefore does not allow for putting appropriate risk mitigation in place.

In view of the above it needs to be considered that a marketing authorisation application under Article 10a of Directive 2001/83/EC must demonstrate that the use of the substance in the relevant indication has been in well-established medicinal use in the European Union for at least 10 years, with a recognised efficacy and an acceptable level of safety. The lack of sufficient and reliable qualitative and quantitative data and subsequent resulting uncertainties do not allow establishing that glycopyrronium bromide has been used in the European Union for the symptomatic treatment of siallorrhea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders with an acceptable level of safety. The application falls therefore short of demonstrating that the requirements of Article 10a of Directive 2001/83/EC are fulfilled.

## *2.7. Pharmacovigilance*

**Detailed description of the pharmacovigilance system**

Due to the aforementioned concerns a satisfactory pharmacovigilance system cannot be agreed at this stage.

## *2.8. Risk Management Plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC provided some comments on version 1.2 as described in the PRAC endorsed PRAC Rapporteur assessment report (appended).

The company implemented the changes as requested. The PRAC rapporteur considered that the RMP version

1.3, which includes the agreed educational materials for healthcare professionals and patient carers to minimise and manage common anticholinergic side effects and prevent the risk of dosing errors and overdose, could be acceptable provided that the benefit/risk balance of this medicinal product is favourable.

The CHMP took note of the Risk Management Plan version 1.3 with the following content but in view of the aforementioned concerns a satisfactory risk management plan cannot be agreed at this stage.

***Safety concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Treatment of patients with severe renal impairment (eGFR <30 ml/min/1.73m$^2$), including those with end-stage renal disease requiring dialysis<br>• Constipation<br>• Urinary retention<br>• Risk of overheating<br>• Overdose<br>• Interactions with other medicinal products |
| Important potential risks | • Cardiac disorders |
| Missing information | • Safety in long-term use, beyond 24 weeks has not been established<br>• Use in patients <3 years<br>• Use in patients with compromised blood brain barrier |

***Pharmacovigilance plan***

Not applicable.

***Risk minimisation measures***

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Treatment of patients with severe renal impairment (eGFR <30 ml/min/1.73m$^2$), including those with end-stage renal disease requiring dialysis. | **Contraindication in Section 4.3 of the SmPC**: that glycopyrronium bromide should be avoided in patients with severe renal impairment (eGFR <30 ml/min/1.73m$^2$), including those with end-stage renal disease requiring dialysis<br><br>**Warning in Section 4.4 of the SmPC**: that due to decreased elimination of glycopyrronium in patients with severe renal impairment, irrespective of the cause (eGFR <30 ml/min/1.73m2), including those with end stage renal disease requiring dialysis, glycopyrronium is contraindicated. Mild to moderate renal impairment has little effect on the elimination of glycopyrronium and no dose adjustment is required. | Not required. |
| Constipation | **Warning in Section 4.4 of the SmPC**: that patients should be assessed for constipation after initiation of drug and after any dose increase<br><br>**Undesirable effects in Section 4.8 of the SmPC**: that constipation was seen very commonly in studies with glycopyrronium and advises the prescriber to alert the carer to this side effect with a caution to reduce the dose in the case of constipation. | A HCP and Care Givers educational card (see Annexes 10 and 11) |
| Urinary retention | **Contraindication in Section 4.4 of the SmPC:** in urinary retention<br><br>**Warnings in Section 4.4 of the SmPC:** that glycopyrronium can cause urinary retentionand it should be discontinued if urinary retention is present.<br><br>**Undesirable effects in Section 4.8 of the SmPC**: states that urinary retention was seen very commonly in studies with glycopyrronium. Additionally it advises the prescriber should alert the carer to the following side effects with advice to stop treatment in the case of urinary retention. It is noted that the following adverse events are known to occur with anticholinergic drugs | A HCP and Care Givers educational card (see Annexes 10 and 11) |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | such as glycopyrronium, due to their pharmacological actions: urinary retention | |
| Risk of Over heating | **Warning in Section 4.4 of the SmPC: th**at glycopyrronium bromide inhibits sweating and patients with pyrexia should be observed closely and the dose reduced if necessary. The patient should not to be exposed to hot or very warm weather.<br><br>**Undesirable effects in Section 4.8 of the SmPC**: pyrexia was commonly reported in studies and advises the prescriber to alert the carer to this side effect with a caution to reduce the dose in the case of pyrexia or hot weather. | Not required. |
| Overdose | **Posology Section 4.2 of the SmPC** advises that dose titrations are conducted in discussion with the carer to assess efficacy and side effects until an acceptable maintenance dose is achieved and that sialorrhoea should be monitored, in conjunction with the carer, to assess changes in efficacy and/or tolerability over time, and the dose adjusted accordingly.<br><br>**Overdose section 4.9 of the SmPC states:** There are no data on overdose of Sialanar in children and that patients, parents and/or caregivers should be counselled to ensure an accurate dose is given each time, in order to prevent the harmful consequences of anticholinergic reactions of glycopyrronium bromide seen with dosing errors or overdose.<br><br>Overdose of glycopyrronium can result in anticholinergic syndrome, produced by the inhibition of cholinergic neurotransmission at muscarinic receptor sites. Clinical manifestations are caused by CNS effects, peripheral nervous system effects, or both. Common manifestations include flushing, dry skin and mucous membranes, mydriasis with loss of accommodation, altered mental status and fever. Additional manifestations include sinus tachycardia, decreased bowel sounds, functional ileus, urinary retention, hypertension, tremulousness and myoclonic jerking.<br><br>Patients presenting with anticholinergic toxicity should be transported to the nearest emergency facility with | A HCP and Care Givers educational card (see Annexes 10 and 11) |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | advanced life support capabilities. Avoid administering ipecac syrup and activated charcoal unless prolonged transport time is anticipated. Removal of toxin from the GI tract can be accomplished in the vast majority of patients with single-dose activated charcoal by mouth or nasogastric tube. Physostigmine salicylate is recommended when tachydysrhythmia with subsequent hemodynamic compromise, intractable seizure, severe agitation or psychosis is present.<br><br>**The PIL** also states that it is important to make sure an accurate dose is given each time, in order to prevent harmful effects of Sialanar seen with dosing errors or overdose. | |
| Interactions with other medicinal products | **Contraindication in Section 4.3:** co-administration with potassium chloride solid oral dose; topiramate, anticholinergic drugs; antispasmodic drugs; such as domperidone and metoclopramide<br><br>**Interactions in section 4.5 of the SmPC:** notes that no studies have been performed and there are limited data available relating to interactions in the paediatric age group and no studies of drug interactions with Sialanar. Advice is given that concomitant use of the following drugs should be avoided: potassium chloride solid oral dose, topiramate, anticholinergic drugs, antispasmodic drugs<br><br>Also advising that concomitant use of the following drugs should be considered with caution: sedating antihistamines, neuroleptics/antipsychotics: (such as phenothiazines, clozapine and haloperidol), skeletal muscle relaxants, botulinum toxin, tricyclic antidepressants and MAOIs, disopyramide, amantadine, nefopam, opioids, digoxin, corticosteroids, nitrates, beta-blockers, levodopa. | A HCP and Care Givers educational card (see Annexes 10 and 11) |
| Cardiac disorders | **Warning in Section 4.4 of the SmPC**: that glycopyrronium bromide should be used with caution in patients with acute myocardial infarction, hypertension, coronary artery disease, cardiac arrhythmias and conditions characterised by tachycardia (including thyrotoxicosis, cardiac insufficiency, cardiac surgery) due to the potential increase in heart rate produced by | Not required. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | its administration. | |
| Safety in long-term use, beyond 24 weeks has not been established | **Method of administration 4.2 of the SmPC**: Placebo controlled efficacy data includes patients with a treatment duration of 8 weeks. An open label study includes efficacy data with a treatment duration of 24 weeks. The recommended maximum duration of therapy is 24 weeks.<br><br>The safety and efficacy of glycopyrronium bromide have been studied over a 6 month period, with 52-56% of the children who were still taking study medication, achieving at least a 3 point decrease on the modified Teacher's Drooling Scale (mTDS) over this time. The well known adverse event profile seen with anticholinergic drugs was demonstrated in children with chronic drooling. No new or different adverse events were seen. There is insufficient safety data beyond 24 weeks to establish the long-term efficacy or safety profile of glycopyrronium in the target population. The recommended maximum duration of therapy is 24 weeks.<br><br>Since children affected by pathological drooling may improve spontaneously, attempts to discontinue treatment should be performed intermittently to evaluate the need for continued treatment. | Not required. |
| Use in children below the age of 3 years | **Posology and method of administration in Section 4.2 of the SmPC**: that due to the lack of data on efficacy and safety glycopyrronium should be avoided in children below the age of 3 years.<br><br>**Contraindication in Section 4.3 of the SmPC**: children below the age of 3 years | A HCP and Care Givers educational card (see Annexes 10 and 11) |
| Use in patients with compromised blood brain barrier | **Warning in Section 4.4 of the SmPC**: Glycopyrronium bromide is a quaternary ammonium member of the anticholinergic class of drugs and as a consequence of its quaternary charge, has limited ability to penetrate the blood brain barrier, but the extent is unknown. Caution should be exercised in children with compromised blood brain barrier. | Not required. |

## *2.9. Product information*

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* However, Due to the aforementioned concerns a satisfactory package leaflet cannot be agreed at this stage.

# 3. Benefit-Risk Balance

***Benefits***

**Beneficial effects**

The benefit of glycopyrronium in alleviating pathological drooling in children with neurological disorders has been demonstrated in two randomised, placebo-controlled clinical trials: The Zeller, 2012a study and the Mier, 2000 study. Both studies were short-term as the treatment duration was 8 weeks.

The pivotal 8-week study in Zeller at al. 2012a conducted with thirty-eight patients demonstrated superiority of glycopyrrolate over placebo in reduction of drooling in children 3-16 years old:

The initial dose was 0.02 mg/kg, which was increased in 0.02 m g/kg increments every 5 to 7 days up to a maximum dose of 0.1 mg/kg (but not to exceed a maximum dose of 3 mg t.i.d, regardless of weight). The responder rate at Week 8 (≥ 3 point improvement on the mTDS) was significantly higher for glycopyrrolate (14/19; 73.7%) than for placebo (3/17; 17.6%) (p = 0.0011), with improvements starting 2 weeks after treatment initiation (52.6% vs. 0%; p=0.00007). The favourable effects of GP on the mTDS were corroborated by results of investigator and patient/caregiver rated global assessments. Due to differences in relative bioavailability between Sialanar (approximately 25% higher bioaviliablility) and the product used in this trial the proposed titration scheme for Sialanar was adapted during the procedure to largely mirror exposure levels obtained during titration in this trial.

Also the study by Mier et al. conducted in thirty-nine children aged 4 years and older with neurodevelopmental conditions and severe sialorrhoea demonstrated superiority of glycopyrrolate over placebo. Doses were increased in 0.6 mg increments in both groups but from different starting doses: 0.6 to 2.4 mg in the lower weight group and 1.2 to 3.0 mg in the higher weight group. Drooling score on the mTDS improved in a linear manner with increasing dose level over the 4-week titration period; scores were 6.0 at dose level 1, 4.5 at level 2, 3.6 at level 3, and 2.6 at level 4. After an additional 4 weeks at the highest individual dose the mean drooling score had decreased further to 2.3.

These two randomised, double-blind studies are supported by a long-term safety study by Zeller at al. 2012b. In this 24-week, open-label study glycopyrrolate was administered to 137 paediatric patients between 3-18 years of age. At Week 24, 52.3% (95% CI 43.7–60.9) of subjects were responders (≥ 3 point reduction on the mTDS). The proportion of responders ranged between 40.3% and 56.7% over the 6 assessment points during the 24 week study period.

**Uncertainty in the knowledge about the beneficial effects**

General uncertainties on the beneficial effects are deriving from the study design and the analysis/reporting of both the Zeller 2012a study and, in particular, the Mier study. Issues relate to the overall study design, blinding, enrichment of study population, population of analysis, imputation method for missing data, reporting of results by age group as well as other aspects which could not be clarified in the context of this bibliographic application. The main efficacy studies were performed with other formulations of GP than Sialanar. The higher bioavailability of Sialanar compared to the product used in the pivotal Zeller studies (Zeller 2012a and Zeller 2012b) was addressed by revising the titration schedule for Sialanar, addressing the concern on the uncertainty on the applicability of the pivotal data to Sialanar.

The two placebo-controlled studies only investigated efficacy in the short-term and although the open-label study Zeller 2012b offers some reassurance about maintenance of the effect over 24 weeks maintenance of efficacy for long term or chronic use could not be substantiated by the available data. The applicant revised the treatment duration during the procedure to a maximum treatment duration of 24 weeks considering the available efficacy data however the treatment is aimed for a chronic condition.

Also in view of the side effects of glycopyrronium, uncertainty remains regarding the overall effect on quality of life (QoL) in this patient group since no data on QoL specific to this treatment and patient population have been presented.

***Risks***

**Unfavourable effects**

Most of the adverse events that occurred more frequently in patients treated with GP than in patients on placebo were typical anticholinergic effects. They included dry mouth/excessive dryness of mouth or secretions, constipation, vomiting, nasal congestion, flushing, behavioural changes, urinary retention and diarrhoea. Overall these events occurred quite frequently in GP treated patient with frequencies ranging from 10 to 40%.

The Mier article reports that 23% of the children treated with GP had behavioural changes. The Blasco article mentions that 13% had behavioural changes while none of the other article mentions this AE as a frequent AE. Further a study in children with hydrocephalus showed that in some children GP crosses the blood brain barrier. Furthermore drowsiness, confusion, somnolence have been reported as adverse effects of GP.

Urinary tract dysfunction including retention are frequent symptoms associated with cerebral palsy. However, urinary retention was not observed in the placebo group in either of the placebo controlled studies but occurred in 13-15% of the patients treated with GP. The high frequency of urinary retention with GP constitutes a major concern.

Pneumonia occurs often in patients with cerebral palsy and was also a frequent adverse event in the Zeller 2012b study and increased with increasing dose, which suggests a causal relationship to GP.

**Uncertainty in the knowledge about the unfavourable effects**

After detailed assessment of the submitted safety data the overall safety and tolerability profile of GP is still associated with significant uncertainties. Insufficient details are provided on the exposed patients to compensate for the small number of patients included in the submitted publications on controlled trials as well as in long-term studies.

In the submitted articles GP has primarily been used in adults and in the paediatric populations as surgery premedication and in the adult population also for the treatment of chronic obstructive pulmonary disease but in different formulations and not as an oral solution. The AE profile established in other populations cannot readily be extrapolated to a patient population of children with neurological disorders which often have considerable comorbidity. Furthermore only single administrations were used with premedication. In contrast, long-term use is expected with Sialanar.

Only the Zeller 2012a (n=38, 20 patients exposed to GP) article offers safety data from a placebo-controlled study where the posology resembles the posology proposed by the Applicant with regard to formulation used, initial dose, increments in dose during titration of the dose and recommendations with regards to administration with or without food.

Information derived from the submitted literature and in particular from the pivotal safety studies is insufficient to conclude on an acceptable safety profile.

It could not be clarified by the applicant if a sufficient number of children in each of the age groups, and in particular within the age group 3-11 have been exposed to GP. This is considered an important uncertainty as the development of children by age category differs. There is no information on neurodevelopment or growth (height and weight).

Furthermore, there is no information regarding the incidence and severity of AE by age group, and if patients in a certain age group had a higher discontinuation rate and at what dose level patients discontinued. As capturing and identifying AEs in children with neurological disorders can be difficult, it is even more important to have a sufficient database size and details on the exposed patients.

In the absence of robust clinical safety data, also the non-clinical data cannot provide sufficient assurance on repeat-use toxicology, reproductive/developmental toxicology, genotoxicity and carcinogenicity. Extrapolation of safety margins to the proposed population are not considered adequate due to lack of toxicokinetic exposure data.

GP, as any anticholinergic, is expected to have cardiac effects. Insufficient information has been provided on pulse rate and blood pressure. Hence, there is uncertainty about the cardiovascular safety of GP in this patient group. Urinary retention was reported with an incidence of 13-15% in the pivotal clinical studies whereas not occurring in the placebo arm and also pneumonia appears to be associated with GP use and there is insufficient information on the severity of these adverse events.

The Sialanar formulation is more bioavailable than the formulation used in the Zeller studies being pivotal for clinical safety. Even though the titration schedule was amended taking into account the higher bioavailability of the Sialanar formulation the generally high PK variability makes it uncertain to what extent the titration and dosing schedule used in the Zeller studies can be safely applied on the use of Sialanar. However, the recommended initial dose and dose titration schedule has been revised taking into account the higher bioavailability of the Sialanar formulation. This uncertainty has therefore been reduced significantly.

Also pneumonia appears to be associated with GP use and there is uncertainty about its clinical significance in children. Furthermore and the clinical significance of the reported CNS effects with GP, in children with neurological disorders is associated with uncertainty.

There are no data on adverse events from placebo-controlled trials with treatment duration longer than 8 weeks and the Applicant has proposed to limit the treatment duration to 24 weeks based on the data from the Zeller 2012b article. Reducing the duration of treatment could in theory reduce the risk of adverse

developmental effects, but many patients will presumably be treated for several individual treatment episodes in view of the chronicity of the underlying conditions.

Furthermore uncertainties on the clinical importance of cardiovascular and CNS effects, urinary retention and the insufficiently characterized safety profile remain and reducing the duration of treatment does not sufficiently address these above concerns.

### *Effects Table*

**Table 23 Effects Table for Sialanar (glycopyrronium bromide) for sialorrhoea (chronic pathological drooling) in children with neurological disorders.**

| Effect | Short Description | Unit | Treatment (glycol-pyrronium) | Control (placebo) | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| mTDS responder | Proportion with ≥3-point improvement at week 8 | n/N (%) | 14/19 (73.7) | 3/17 (17.6) | p = 0.0011 | Zeller et al, 2012a |
| mTDS | Mean improvement at week 8 | | 3.94 | 0.71 | P < 0.0001 | Zeller et al, 2012a |
| Investigator global assessment | Proportion rated as worthwhile | % | 84.2 | 41.2 | p = 0.0140 | Zeller et al, 2012a |
| Patient/care giver global assessment | Proportion rated as worthwhile | % | 100% | 56.3 | p = 0.0017 | Zeller et al, 2012 |
| Drooling score | Mean score following treatment | | 1.85 | 6.33 | p < 0.001<br>Study setup very different from recommended use of Sialanar | Mier et al, 2000 |
| Drooling score, dose response | Mean score after 4 weeks at highest dose by dose level | | Level 1: 6.0<br>Level 2: 4.5<br>Level 3: 3.6<br>Level 4: 2.3 | | No CI or p-values reported | Mier et al, 2000 |
| Drooling score responder, dose responder | Proportion with ≥4-point improvement by dose level | % | Level 1: 12<br>Level 2: 38<br>Level 3: 54<br>Level 4: 81 | | No CI or p-values reported | Mier et al, 2000 |
| **Unfavourable Effects** | | | | | | |
| Dry mouth and Excessive dryness of mouth or secretions | | % | 18-40 | 0-11 | | Zeller et al, 2012a and Mier et al, 2000 |
| Constipation | | % | 18-30 | 0-22 | | Zeller et al, 2012a and Mier et al, 2000 |
| Vomiting | | % | 10-30 | 0-11 | | Zeller et al, 2012a and Mier et al, 2000 |

| Effect | Short Description | Unit | Treatment (glycol-pyrronium) | Control (placebo) | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Nasal congestion | | % | 10-30 | 3-5 | | Zeller et al, 2012a and Mier et al, 2000 |
| Flushing | | % | 10-25 | 3-17 | | Zeller et al, 2012a and Mier et al, 2000 |
| Behavioural changes | Includes drowsiness, restlessness, overactivity, short attention span, frustration, irritability, mood changes, temper outbursts, explosive behaviour, excessive sensitivity, seriousness, sadness, frequent crying episodes, fearfulness. | % | 23 | 3 | | Mier et al, 2000 |
| Urinary retention | | % | 13-15 | 0 | | Zeller et al, 2012a and Mier et al, 2000 |
| Diarrhoea | | % | 10 | 3 | | Mier et al, 2000 |

***Benefit-risk balance***

**Importance of favourable and unfavourable effects**

Alternative treatment options, non-pharmacological and pharmacological, for sialorrhoea are limited and at present there is insufficient evidence to be able to distinguish between these different approaches, though it is clear that none of them is completely successful in all individuals. Possible detrimental effects of uncontrolled drooling include irritated and macerated skin, dehydration and lowering of self-esteem. The favourable effects of GP on pathological drooling in children with neurological disorders are considered possibly clinically relevant.

The lack of selectivity of anticholinergics can lead to widespread, undesirable, and often poorly tolerated central and peripheral effects, including restlessness, irritability, drowsiness, constipation, urinary retention, and flushing. Chronic urinary retention can lead to damage to the bladder by overextension. Additionally, there is a risk of reflux leading to tubular atrophy and, eventually, irreversible renal injury.

Since the patients with CP may suffer from fluctuating daily living capacity or may also suffer from various mental disorders, neurological adverse effects are likely to be completely unrecognized or under-reported in the clinical studies. Decrease of daily activities/quality of life may be a negative consequence of these adverse events.

**Benefit-risk balance**

The efficacy of Sialanar in alleviating pathological drooling in children with neurological disorders need to be weighed against many and significant uncertainties in terms of safety due to the lack of appropriate data on safety and tolerability profile.

***Discussion on the benefit-risk balance***

Taken together, submitted data supports short term efficacy on pathological drooling in patients as of the age of three years. Although the open-label study Zeller 2012b offered some reassurance about maintenance of the effect, the two placebo-controlled studies only investigated efficacy in the short-term. None of the studies supported chronic use of GP in paediatric subjects with sialorrhoea from a clinical efficacy perspective and the indication was revised during the procedure to a maximum treatment duration of 24 weeks considering the available efficacy data.

The overall safety and tolerability profile of Sialanar in the claimed indication comprising chronic use in neurologically impaired paediatric patients is associated with significant uncertainties due to the lack of appropriate data leading to an insufficient characterisation of the safety profile.

There are insufficient details in the submitted literature including controlled trials as well as long-term studies to draw reliable conclusions on safety for the claimed indication. Furthermore the number of patients exposed in the claimed indication is limited. Due to the absence of data in patients younger than three years the earliest age for treatment in the indication was increased from 2 to 3 years during the procedure but an insufficient characterisation of the safety profile by age group in the remaining age subsets remains (i.e. in the age groups 3-11 and 12-18 years).

It is uncertain if the plasma concentrations of Sialanar in children and adolescents with neurological disorder could cause clinically relevant effects on blood pressure and heart rate. There is no information in any of the articles on HR increases with GP treatment in children with neurological disorders. Additionally, there is insufficient information regarding effects on blood pressure. Hence, there is uncertainty about the cardiovascular safety of GP in this patient group.

Urinary retention was reported with an incidence of 13-15% with GP in randomized controlled clinical studies whereas not occurring in the placebo arm and there was no information provided on the severity of the episodes of urinary retention nor if it was associated with an increased incidence of urinary tract infections. Also pneumonia appears to be associated with GP use and there is insufficient information on the severity of these adverse events.

CNS effects have been reported with GP, and their significance in children with neurological disorders is associated with uncertainty. Additionally, there is no information on neurodevelopment or growth (height and weight) which may be affected particularly when treatment is applied chronically or in repeated episodes.

Reducing the duration of treatment is considered not to sufficiently address the above safety concerns as many patients will presumably be treated for several individual treatment episodes in view of the chronicity of the underlying conditions.

Although the condition can be very unpleasant for the affected children and their parents and caregivers, it is not fatal or severely debilitating. While some of the unfavourable effects – as they are currently known – might be clinically manageable, significant uncertainties remain with regard to important unfavourable effects, in particular per age group which may remain unknown and / or not being known in their severity.

Furthermore and in view of the above uncertainties on side effects, it could not be demonstrated by the applicant if the effect of the treatment – decrease of drooling – provides improvement in the quality of life of the patients comprised in the claimed indication.

Finally a marketing authorisation application under Article 10a of Directive 2001/83/EC must demonstrate that the use of the substance in the relevant indication has been in well-established medicinal use in the European Union for at least 10 years, with a recognised efficacy and an acceptable level of safety. The lack of sufficient and reliable qualitative and quantitative data and subsequent resulting uncertainties do not allow establishing that glycopyrronium bromide has been used in the European Union for the symptomatic treatment of siallorrhea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders with an acceptable level of safety. The application falls therefore short of demonstrating that the requirements of Article 10a of Directive 2001/83/EC are fulfilled.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy for Sialanar in the treatment of sialorrhoea (chronic pathological drooling) in children aged 3 to <18 years with neurological disorders the CHMP considers by consensus that the safety of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

Whereas

- The overall safety and tolerability profile of Sialanar in the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders is not appropriately characterised. There are significant safety concerns due to the aimed chronic use of Sialanar in the paediatric population affected by the underlying conditions, in particular on the risks of cardiovascular effect, developmental effects, urinary retention and CNS effects. These uncertainties are a major concern in view of the target population, which cannot be addressed adequately by a reduction of the duration of treatment due to the chronicity of the underlying conditions or by warnings and precaution statements in the Product Information.
- The lack of adequate non-clinical data in support of the claimed indication does not provide sufficient assurance on repeat-use toxicology, reproductive/developmental toxicology, genotoxicity and carcinogenicity. Extrapolation of safety margins to the proposed population are not considered adequate due to lack of toxicokinetic exposure data;
- A marketing authorisation application submitted under Article 10a of Directive 2001/83/EC must demonstrate that the use of the substance in the relevant indication has been in well-established medicinal use for at least 10 years in the European Union, with a recognised efficacy and an acceptable level of safety. The lack of sufficient and reliable qualitative and quantitative data and subsequent resulting uncertainties do not allow to establish that glycopyrronium bromide has been used in the European Union for the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders with an acceptable level of safety. The application falls therefore short of demonstrating that the requirements of Article 10a of Directive 2001/83/EC are fulfilled;

- Having considered above the safety profile, it has also not been demonstrated that Sialanar is associated with any improvement in the quality of life in the claimed indication.

the CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety of the above mentioned product is not sufficiently characterized and does not outweigh the benefit for the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders. The CHMP therefore considers that the overall benefit/risk balance is unfavorable and recommends the refusal of the granting of the marketing authorization for Sialanar.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, cannot be agreed at this stage.

# 5. Re-examination of the CHMP opinion of 28 April 2016

Following the CHMP conclusion that Sialanar was not approvable as the safety of the above mentioned medicinal product is not sufficiently demonstrated; the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

***Detailed grounds for re-examination submitted by the applicant***

The applicant presented their detailed grounds in writing and at an oral explanation. A summary of the applicant´s grounds for re-examination is presented below.

## *Ground #1*

- The overall safety and tolerability profile of Sialanar in the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders is not appropriately characterised. There are significant safety concerns due to the aimed chronic use of Sialanar in the paediatric population affected by the underlying conditions, in particular on the risks of cardiovascular effect, developmental effects, urinary retention and CNS effects. These uncertainties are a major concern in view of the target population, which cannot be addressed adequately by a reduction of the duration of treatment due to the chronicity of the underlying conditions or by warnings and precaution statements in the Product Information.

## Applicant's grounds for re-examination: Point 1

The CHMP have concerns over the lack of full characterisation of the overall safety and tolerability profile of Sialanar in the symptomatic treatment of sialorrhoea in children and adolescents aged 3 to <18 years with neurological disorders. The specific safety concerns result from the aimed chronic use of Sialanar in the paediatric population affected by the underlying conditions, in particular on the risks of cardiovascular effect, developmental effects, urinary retention and CNS effects. These uncertainties are a major concern to CHMP in view of the target population, and they are of the belief that the concerns cannot be addressed adequately by a reduction in the duration of treatment due to the chronicity of the underlying conditions or by warnings and precaution statements in the Product Information. This document collates and discusses the data contained in the PUMA Application for each of the outstanding areas with the aim of providing the necessary information to justify the presence of adequate safety information for each of the specific points of concern. The Applicant believes that the data from controlled and open clinical studies, supported by an extensive dataset from CPRD (the world's largest database of real-life patient data including histories, diagnoses and drug treatments) provides unequivocal proof of the safety of GP in the target population and justifies a positive opinion on the licence application. Safety overview Safety data is covered in detail in m2.5.5, which should be read in conjunction with this document. The data show that the majority of the AEs occurring more frequently in patients treated with GP than in patients on placebo, were typical anticholinergic effects. They included dry mouth, constipation, vomiting, nasal congestion, flushing, behavioural changes, urinary retention and diarrhoea. These events occurred with frequencies ranging from 10 to 40% in the GP group.

For most of the events, a difference from placebo was observed in both placebo controlled studies (Zeller, 2012a and Mier, 2000). However, an excess incidence of behavioural changes and diarrhoea in the GP group was reported only in the Mier study. There are no data on adverse events from placebo-controlled trials with treatment duration longer than 8 weeks. The DRI study compared 2 active drugs (GP and hyoscine) over a period of 12 weeks and confirms the known safety profile plus an improved tolerability of GP over hyoscine (Parr, 2016).

Treatment emergent AEs have been extensively examined from the data in CPRD and are discussed in detail in m2.5.5.3 with the majority of treatment episodes lasting less than 6 months. Comparing AEs in the treated population versus the full cohort, the most common infections were of the respiratory tract (381/2739) with urinary tract infections accounting for 33/219 events. The most common GI events were constipation (72/450) and vomiting (67/392). The most common events for respiratory, nervous, general and skin are cough (228/1542), epilepsy (80/536), pyrexia (27/247) and rash (58/392). The events and their frequencies are entirely consistent with those seen both in this population and in relation to use of GP in the clinical trials.

Occurrence of AEs is dose-related, hence the need to apply a dose titration scheme as proposed by the Applicant and used in current clinical practice. The dose titration is based on the patient's efficacy response balanced against the occurrence of adverse events. The adverse events are well-known anticholinergic effects, which can all be assessed by the caregiver in discussion with the prescriber and the PIL contains detailed instructions on what undesirable effects to look for and how to manage them.

Contraindications to use are, hypersensitivity to GP or any of the excipients, use in children below the age of 3 years, glaucoma, severe renal impairment (eGFR <30 ml/min/1.73m2), including those with end-stage renal disease requiring dialysis, history of intestinal obstruction, diarrhoea, ulcerative colitis, paralytic ileus, pyloric stenosis, myasthenia gravis, pregnant or lactating women. In addition, the following drugs must not be co-administered with glycopyrronium; potassium chloride solid oral dose, topiramate, anticholinergic and antispasmodic drugs. Patients with mild to moderate renal impairment (eGFR >30 ml/min/1.73m2) will be given a 30% dose reduction.

Products containing the active ingredient have been licensed in Europe for many decades. Pharmacovigilance data have not revealed any special safety concerns associated with use of GP during that period, including its long-term use in 'special' preparations for the treatment of sialorrhoea.

Safety information on areas of concern to CHMP

Chronic use

Duration of GP treatment in the placebo-controlled trials (Zeller et al, 2012a, Mier et al, 2000) was 8 weeks and in the comparator controlled trial (Parr, 2016), 12 weeks. Exposure in the open-label study (Zeller et al, 2012b) was 24 weeks. All studies used a slow dose titration scheme based on the body weight of the child. The clinical data support the safety in this population up to 24 weeks. However, it is clear that GP will be used in a proportion of patients for longer than the 24-week period covered by the clinical data. Therefore, given the lack of safety data beyond 24 weeks, the Applicant has conducted a detailed assessment of safety information available in the CPRD database, to understand the clinical history of children with sialorrhoea treated with GP (m2.5.5.6). The purpose of the CPRD study was to assess all children in the database who had a prescription for GP and/or a diagnosis of drooling, resulting in a final dataset of 3,672 children. Analysis of the data showed:

• The vast majority of patients, 2,512 (68.5%), received no treatment associated with a drooling diagnosis.

• 428 (82%) of the 521 patients who received at least one prescription for GP were being treated for sialorrhoea.

• Using a gap in treatment episodes of 45 days, 152 (35.7%) patients had a single treatment episode, 345 (81%) had up to 6 separate treatment episodes, 48 (11.3%) had between 7 and 12 separate episodes with the remainder having between 13 and 49 separate treatment episodes.

• The mean duration of all treatment episodes was 4.8 months ranging from 2 to 92 months.

• The cohort of 428 patients treated with GP for sialorrhoea provided information on a population equivalent to 26,089 children age 3-17 years covering 24,684 patient-years.

• Within this period, children received treatment with GP for an equivalent of 435 patient-years.

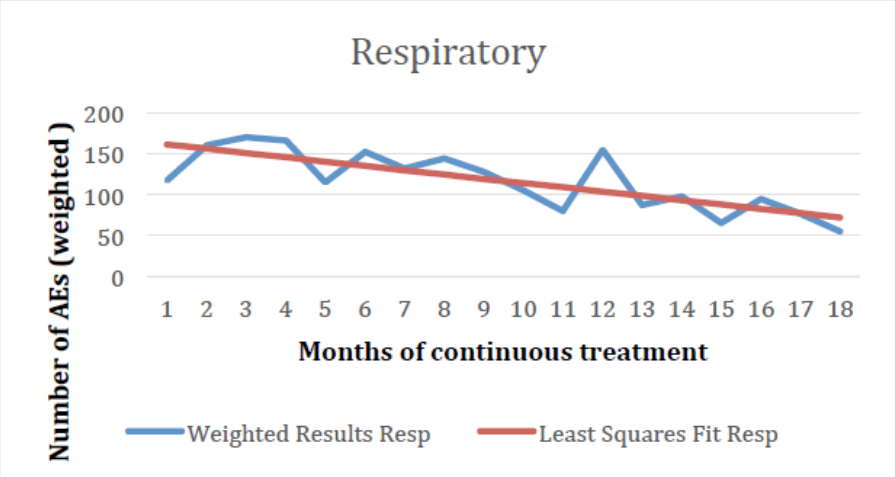
• In total 1,797 treatment episodes occurred of which 1,565 (87.1%) lasted up to 6 months with a further 170 (9.5%) lasting from 7 to 18 months. The remaining 62 (3.4%) treatment episodes ranged from 19 to 92 months.

The data from the CPRD allows meaningful calculations for the effect of treatment duration on the more common AEs relating to respiratory infection, cough, pneumonia and constipation. Weighting is used to compare AE incidence with the number of months into a GP treatment that a particular AE occurred, thus counterbalancing the decrease in the number of treatment windows that remain open as time goes on. As such, the incidence figures presented do not represent the actual number of treatment windows that remain open as time goes on. As such, the incidence figures presented do not represent the actual number of incidences of AEs from month 2 onwards. However the weighting allows trends to be observed in the figures that would otherwise be invisible. As the number of open windows decreases, the number of AE incidences will fall, but as the weighting factors are inversely proportional to the AE decrease. The weighted incidence figures would remain flat where the duration of GP treatment has no influence on incidence of AEs. Therefore trend lines drawn over a graph of the AE incidences can show whether GP use has a positive, negative or neutral effect on the incidence rates of particular adverse events. Analysis of the data shows that in the weighted AE trends in patients treated with GP for sialorrhoea, as treatment duration increases, the incidence of the more commonly occurring AEs, respiratory infection, cough, pneumonia and constipation decreases Figure below (a-d), presented for 18 months treatment duration. This is true for all treatment durations although the low numbers beyond 18 months do not allow accurate calculations due to a high likelihood of sampling error. This evidence builds on the safety data, up to 6 months, available from clinical studies and provides confidence that longer treatment duration, beyond 6 months, does not result in an increased incidence of AEs.

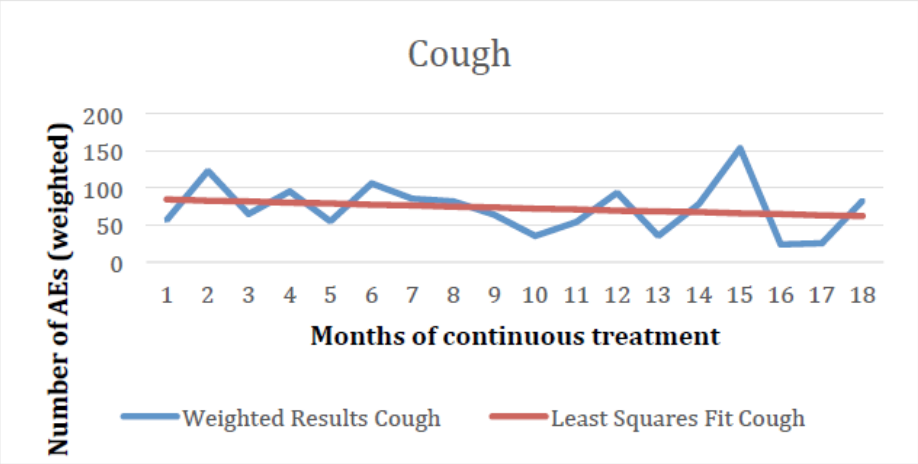
**Figure 4**

**Figure 1 Weighted incidence of AEs versus time on GP treatment**

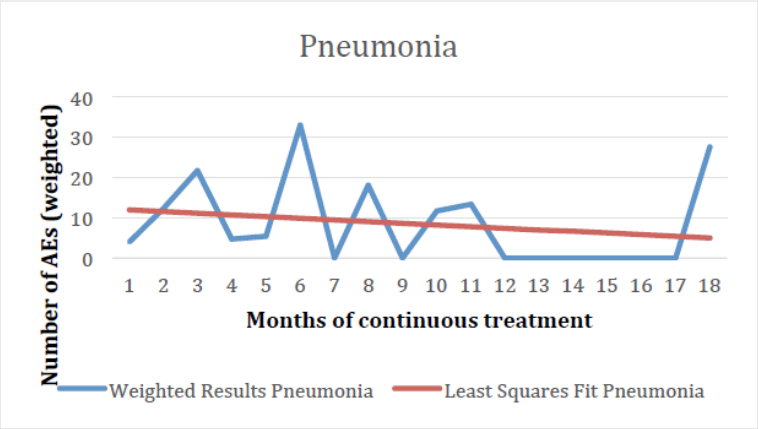
**1a Respiratory infection**



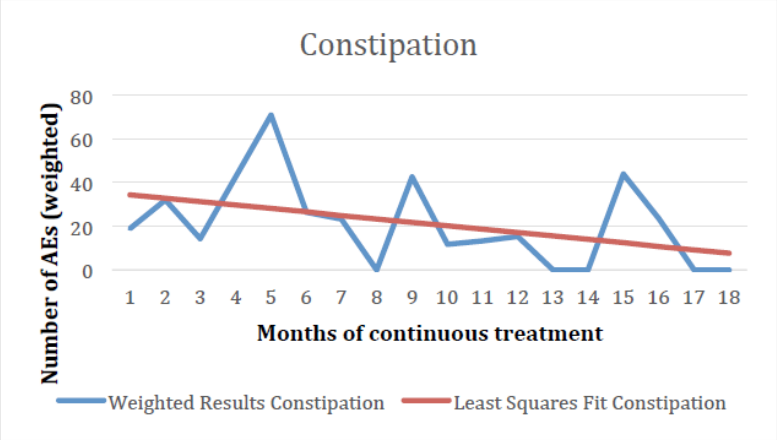

**1b Cough**



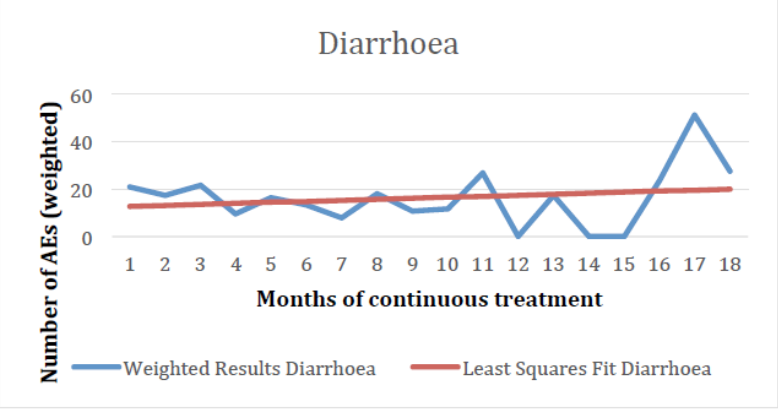
**1c Pneumonia**




**1d Constipation**




**1e Diarrhoea**



The data for diarrhoea Figure 1 (e) shows a marginal increase in incidence with time, but since this is based on a single event at treatment-month 18 (with no episodes of diarrhoea between 12 and 18 months) it is highly likely to be a result of sampling error. Reducing the weighting (from 2 to 1 event) reverses the line to show a decrease in incidence of diarrhoea over time. Trends in AEs for CV and urinary retention are not presented since the very small numbers of events dramatically increases the chance of sampling errors. The data from the CPRD shows that the vast majority of children (87.1%) have treatment episodes lasting up to 6 months (m2.5.5.2). The evidence from CPRD showing a decline in the incidence of common AEs with time in this population provides comprehensive support for the safe use of GP for periods longer than 6 months. As such, there is no justification for inclusion of a maximum 6-month treatment duration in the SmPC. As pointed out by the CHMP and shown in CPRD, a small proportion of children are currently, and will continue to be, treated for periods longer than 6 months. The available evidence provides reassurance that this is a safe practice where there is a clinical need and the benefit/risk ratio is positive.

Age

Module 2.5.5.9 discusses the effects of age on the incidence of AEs in detail. The unfavourable effects seen with GP in the target population are consistently seen as those relating to an effect on anticholinergic receptors. Information in the published clinical studies does not allow an interpretation of any differences in AEs in younger versus older children. Nevertheless, there are a significantly greater proportion of younger children across all studies and hence the majority of the available safety data is on younger children. Therefore the clinical study data is highly representative of the younger population. The data in the CPRD have been examined to assess the effect of age on incidence of AEs. CPRD supports the known position that AEs per se are more common in younger children compared to older children, whether or not they are on treatment with GP. The data from this extensive, real-life database demonstrates that in the treated population pneumonia and constipation have a greater incidence of AEs in younger versus older children with a somewhat smaller increase between the two age ranges for respiratory infection, cough and diarrhoea (m2.5, Table 22). The number of occurrences of urinary retention and cardiac events in CPRD are extremely low and as such reliable conclusions cannot be drawn. If taken on face value the data may indicate an increase in urinary retention in the treated older child versus the younger child and for cardiac events could indicate an increase in events in the older child versus the younger child whether treated with GP or not, but given the low numbers this cannot be confirmed.

The known difference in AEs in younger versus older children per se, is borne out by the available data from CPRD, however the safety profile from clinical studies, as reflected in the SmPC, provides information from all data sources with a default to the use of higher figures where the information is conflicting. The wording in the SmPC captures any difference in AE potential between the age groups and is deemed appropriate information for the prescriber. The SmPC states, “Younger children may be more susceptible to adverse events and this should be borne in mind when any dose adjustments are carried out.”

Cardiovascular system

Module 2.5.3.9.3.1 discusses the CV pharmacodynamic effects of GP in detail. The CV effects of anticholinergic drugs are well understood and the effects of GP have been comprehensively investigated (changes in HR, BP and cardiac rhythm) in a series of studies in paediatric and adult populations (m2.7.2.2.2). The plasma concentration of GP required for effective vagolysis has been determined to be at least 10 µg/L. In studies in children by Rautokorpi et al, 1994 and Rautokorpi et al, 1998 plasma concentrations following a 5 µg/kg i.v. dose of GP only briefly exceeded this concentration immediately following administration (m2.7.2, Figure 1). Conversely they never exceeded ~0.3 µg/L following a 50 µg/kg oral dose (m2.7.2, Figure 2). Significant changes from baseline in HR were not seen in any paediatric age

group in either study (m2.7.2, Figure 17). In addition no changes in BP were observed after GP by either route of administration (m2.7.2, Figure 18). Evidence suggests that at the low plasma concentrations of GP likely after oral administration modest and generally clinically insignificant decreases in HR may be observed (m2.7.2, Figure 27). Conversely, since induction of a vagolytic effect requires a plasma concentration of 10 µg/L, this is unlikely to be a significant issue for most patients. In study PRO/GLY/001, the maximum plasma concentration after 2 mg (~0.03 mg/kg) GBOS in adult volunteers occurred between 3 and 7 hours post dose, reaching a maxima of ~1000 pg/mL (i.e. 1 µg/L); half that following a corresponding dose of Cuvposa (m2.7.2 Figure 6). The highest dose of GBOS (0.1 mg/kg) in the Applicant's proposed posology is 3.3 fold higher than the average dose (in mg/kg terms) tested in PRO/GLY/001. It is therefore conceivable, given the variability in exposure to GP after oral administration, that some paediatric patients at the highest dose(s) may briefly attain a plasma concentration of GP sufficient to cause a vagolytic effect. However, if concentrations of this magnitude are achieved, they are likely to be very transient and have clinically insignificant effects on HR.

Irrespective of treatment with GP, children with CP frequently have concurrent cardiac abnormalities, higher HR and more ECG abnormalities than normal controls. The PK simulations performed for Sialanar in the youngest target population demonstrate that the expected GP Cmax at steady state is far below the safety threshold of 10 µg/l generally considered for GP in relation to possible cardiovascular AEs.

Tachycardia is a recognized and well-known effect of anticholinergic drugs and is currently the subject of spontaneous reports with existing formulations of GP. No events related to heart rate are reported in the available clinical studies, suggesting that increases in HR, should they have occurred were not clinically significant (Zeller, 2012a and b, Mier, 2000 and Parr, 2016). Five episodes of tachycardia are reported in the full cohort of children in CPRD, with 2 reported within 30 days following a GP prescription. The data does not support a clinically significant effect on HR in the target population.

There were no events of raised BP recorded in the clinical studies in the target population, (Zeller, 2012a and b, Mier, 2000 and Parr, 2016) nor in the CPRD. The data does not support a hypertensive effect of GP in the target population.

Zeller et al performed electrocardiogram (ECG) assessments in both studies and showed there were no significant effects on atrio-ventricular conduction as measured by the PR interval, or depolarization as measured by the QRS duration, at the doses of GP administered in these clinical trials (m2.7.4.2.1.5.3.2). Direct comparison of the simulated plasma levels of GP after the administration of Sialanar in the different paediatric age ranges with the PK observations reported by Drollmann et al (2014) concludes that the occurrence of QT prolongation in the target population is highly unlikely. The data does not support an effect on QT interval with GP in the target population.

Nevertheless, despite the evidence suggesting minimal or no CV AEs due to GP in the target population, given the known CV effects of GP at the high doses used during anaesthetic treatment the following statement has been added to the SmPC: "Glycopyrronium is known to have an effect on heart rate and blood pressure at doses used during anaesthesia although clinical trials in children with chronic drooling have not shown this effect. An effect on the cardiovascular system should be considered when assessing tolerability".

Central nervous system

Module 2.5.5.3.5 discusses the effects of GP on the CNS in detail, with particular attention to behavioural effects. GP has limited ability to penetrate the blood brain barrier and studies show low or absent concentrations of GP in the CSF, unless in the presence of a compromised BBB.

Clinical data on the use of GP in the target population provides inconsistent information on the occurrence of behavioural adverse events. In the studies by Zeller et al 2012a and Zeller et al, 2012b, centrally mediated side effects appear to have been limited in occurrence. Module 5.3.5.3, section 6.2.4 shows the following behavioural AEs and the % of subjects in which they occurred in the open-label study (Zeller, 2012b): irritability (5.8%); restlessness (3.6%); insomnia (2.2%; intentional self injury (2.2%); agitation (1.5%); crying (1.5%); altered mood (1.5%); aggression (0.7%).

In the study by Mier et al, 2000, 23% of subjects had behavioural changes although the exact nature of these changes is not specified. Parents were questioned on a weekly basis about the presence of any AEs from a pre-specified list of possible AEs. Amongst the possible 'behavioural' AEs were: restless, overactive, or short attention span; easily frustrated, irritable; rapid mood changes; temper outbursts, explosive behaviour; overly sensitive, serious, sad, cries easily, fearful.

The mean dose of GP in the study by Mier et al, was 0.11 mg/kg and the maximum 0.2 mg/kg per dose, more than 2-fold higher than the proposed maximum Sialanar dose. Bioavailability of GP from the extemporaneous capsules used in the study is unknown, so systemic exposure relative to Cuvposa or the Applicant's product cannot be determined. However, given the high doses used in this study in some subjects, it is perhaps unsurprising that behavioural changes were observed in some subjects, although a link between maintenance dose and occurrence of AEs was not assessed.

Behavioural changes noted in the study by Blasco et al, (1996) were all stated to be irritability.

The low affinity for GP to cross the blood brain barrier, compared to other anticholinergic drugs is clearly seen in the DRI study (Parr, 2016). In a 12-week comparison with hyoscine in the treatment of children with neurodevelopmental disabilities and chronic drooling, unpredicted side effects leading to withdrawal showed hyoscine to be associated with; ataxia (3), hyperactivity (2), hypotonia/floppiness (1) and increased seizure activity (1); while glycopyrronium was associated with 1 episode of hyperactivity.

AEs relating to behavioural problems were seen infrequently in CPRD in relation to GP treatment. Within the treatment window and in the lifetime of the patient respectively they include abnormal behaviour 2/22, agitation 3/9, anxiety 3/9, emotional distress 4/8 and irritability 1/16. If changes in psychiatric or behavioural events were seen following the introduction of GP treatment, they would be reported to the prescribing doctor, and therefore recorded in CPRD, particularly given that carers of these patients are attuned to the child's normal patterns of behaviour.

The low incidence of behavioural problems in this population was supported by verbal evidence presented by Dr Richard Hain (practising clinician and author of several reference texts on palliative care) during the OE Meeting on 31st March 2016. Dr Hain confirmed the position that in his extensive clinical experience there is a lack of behavioural issues seen in relation to GP treatment in this population.

Based upon the data in the public domain it is not possible to determine if any of the reported centrally-mediated AEs were related to the treatment or the underlying condition e.g. irritability is a known complication of CP related to pain from contractures. In addition, in the Mier publication AEs in the placebo period were not reported, and the studies by Blasco et al and Zeller et al, 2012b were both single arm in design.

In summary, all of the available clinical data suggests that undesirable centrally mediated side effects are infrequent although they may occur in a small proportion of patients, especially at higher doses of GP and in those with compromised BBB. The specific behavioural changes mentioned in the published studies have

been included as possible adverse events in SmPC section 4.8, which also includes the following warning in section 4.4, SmPC:

*"Glycopyrronium bromide is a quaternary ammonium member of the anticholinergic class of drugs and as a consequence of its quaternary charge, has limited ability to penetrate the blood brain barrier. Nevertheless, caution should be exercised in children with compromised blood brain barrier."*

Adverse events relating to changes in behaviour are covered in the PIL, which as well as listing the known behavioural changes states:

"Tell your doctor if you notice any behavioural changes in the child".

Neurodevelopment

Module 2.5.5.3.6 discusses the effects on neurodevelopment in detail. The Applicant has not identified any reports in the scientific literature of adverse effects of GP on neurodevelopment. By 3 years of age healthy children would be expected to have a sufficiently well-developed BBB and GP, when given in the doses proposed by the Applicant, would not be expected to result in neurodevelopmental effects. There were no reports of AEs related to neurodevelopment, including growth (weight and height), in the DAP submitted as part of the application (MHRA, 2014), and none have been reported in the post-marketing data included in the product information for Cuvposa. CPRD does not give any indication of effects of GP on neurodevelopment including growth. Given that GP has been in continuous use for more than 10 years in the UK and often covering many years of a patient's life, without any concern being expressed relating to adverse effects on neurodevelopment or growth, the Applicant considers such effects to be highly unlikely to occur with Sialanar.

Urinary retention

Module 2.5.5.3.3 discusses the effects on the renal system in detail. Urinary retention is a known complication of anticholinergic treatment, with 3 cases (15%) occurring in the placebo-controlled study (Zeller, 2012a). In CPRD a total of 2 events of urinary retention occurred within the 30-day window following treatment with GP compared to 8 events in the total population. Despite urinary retention being a known complication of severe neurodevelopmental disability plus its known association with anticholinergic drugs, it was recorded infrequently in this dataset. Analysis of the individual patient histories shows that where urinary retention occurred whilst a patient was treated with GP, (2 incidences) treatment was withdrawn within a narrow time period following the event.

CPRD records significant events presenting to a general practitioner during the lifetime of the patient and events will generally occur with a lower frequency compared to randomised clinical trials. In the case of urinary retention, the parent or carer is highly likely to know how to manage its occurrence and as such it is less likely to be reported as a new adverse event when it occurs.

The SmPC advises that urinary retention is a known adverse event and treatment with GP should be stopped if urinary retention occurs. Evidence from CPRD shows GP treatment withdrawal in the event of an episode of urinary retention to be current clinical practice.

Pneumonia

Module 2.5.5.3.2 discusses the effects on the respiratory system in detail. Pneumonia is a known complication associated with severe mental disability. Data from CPRD shows that 28/106 (26.4%) episodes of pneumonia occurred whilst the patients were being treated with GP. Detailed analysis of the individual patient histories shows that of these 28 episodes, treatment with GP was discontinued within 40 days of the

event in 75% of cases. Treatment was continued, often for many months in 25% of cases, with concurrent resolution of the pneumonia. The SmPC advises that pneumonia is a known adverse event and treatment with GP should be discontinued if it occurs. CPRD data provides evidence that this approach is used in current clinical practice in 75% of cases, suggesting that GP is only continued where it is deemed to be clinically appropriate.

Summary of the safety information on areas of concern to CHMP

The following summarises the data provided to justify the position that safety data has been sufficiently characterised in terms of chronic use, age, cardiovascular effect, developmental effects, urinary retention and CNS effects.

• From the available data there appears to be an inverse association between continued use of GP and incidence of AEs.

• Age is known to affect the incidence of AEs with younger children being more susceptible to AEs in general. CPRD supports this position, showing more AEs in younger children per se, and more AEs in younger children treated with GP for sialorrhoea than in older children.

• AEs can be effectively managed through optimising dose to balance efficacy with tolerability

• AEs only lead to treatment withdrawal in a small percentage of subjects (Parr, 2016).

• The significant adverse events of urinary retention, constipation and pneumonia are associated with use of GP, as evidenced by clinical trials and CPRD data.

These events have the potential for significant clinical implications and evidence from CPRD suggests that treatment discontinuation is the current clinical practice.

• The Applicant has included urinary retention, constipation and pneumonia in the SmPC as adverse events requiring treatment discontinuation should they occur.

• There is no information in the published literature or in CPRD to suggest an effect of GP on neurodevelopment or growth (height and weight). Cerebral palsy and other neurodevelopmental disabilities are known to be associated with reduced growth and difficulty in feeding often means the children are underweight for their age.

• The SmPC includes a statement that the effects on growth and neurodevelopment are unknown and no studies have been conducted to specifically address such an effect.

The available data conclusively support the Applicant's position that no new or unexpected events are evident despite long-term treatment with GP in many patients. The AEs known to occur can be effectively managed through dose titration or treatment withdrawal in line with current clinical practice.

Given the weight of the available safety data m2.5.5, including that from the extensive, real-life clinical histories available through CPRD, it is evident that the safety of GP in the Applicant's product for the proposed indication has been adequately characterised in particular for chronic use, age, CV effect, developmental effects, urinary retention and CNS effects.

### *Ground #2*

- The lack of adequate non-clinical data in support of the claimed indication does not provide sufficient assurance on repeat-use toxicology, reproductive/developmental toxicology, genotoxicity and

carcinogenicity. Extrapolation of safety margins to the proposed population are not considered adequate due to lack of toxicokinetic exposure data; (Point 2)

## Applicant's grounds for re-examination: Point 2

The CHMP are concerned about the lack of adequate non-clinical data in support of the claimed indication and do not consider there to be sufficient assurance on repeat use toxicology, reproductive/developmental toxicology, genotoxicity and carcinogenicity. In addition, extrapolation of safety margins to the proposed population are not considered adequate due to lack of toxicokinetic exposure data.

The following is a summary of the available data on the points of concern which must be read in conjunction with m2.4 and m2.5, and includes the relevant clinical data from the CPRD analysis. Given the pre-clinical evidence available and the extensive body of clinical evidence, the Applicant remains of the position that further nonclinical studies would not provide any new data that would change the efficacy, safety or tolerability profile of Sialanar in the target population. Module 2.4 provides details of the full non-clinical package

**Repeat use toxicology**

According to the Guideline on the non-clinical documentation for mixed marketing authorization applications, CPMP/SWP/799/95, 2005, single dose and repeated dose toxicity, as well as local tolerance investigations are normally not necessary. Likewise pharmacological investigations including safety pharmacology and pharmacokinetics are normally not necessary.

A repeat dose oral toxicity study in dogs with administration of dose levels of 4, 16, and 64 mg/kg for up to 27 weeks was associated with pharmacological effects, but no overt toxicity; although there is limited experimental detail. In repeated dose toxicity studies with oral and inhalation drug administration in mice, rats, and dogs, mainly an exaggerated PD activity was seen at high dose levels but there were no clear toxic effect on any organs or tissue that was not associated with the PD. The lowest NOAEL with inhalation was determined in a study in dogs with daily drug inhalation for 39 weeks at 0.02 mg/kg bw.

The lowest NOAEL with oral drug administration was determined in mice at 30 mg/kg bw, although administered for 7 days only. As drug absorption from the gastrointestinal tract is low, and local effects in the lung were observed upon inhalation, the NOAEL from oral drug administration appears more relevant. The dose level of 30 mg/kg bw in the mouse corresponds to a human equivalent dose of 30 mg/kg / 12.3 = 2.44 mg/kg bw.

The safety profile observed in the long-term animal studies is observed in both the open-label safety study over 24 weeks (Zeller RS et al, Safety and efficacy of glycopyrrolate oral solution for management of pathologic drooling in paediatric patients with cerebral palsy or other neurologic conditions. Ther Clin Risk Manag 2012, 8:25-32) and in the data from the CPRD. GP has been used extensively in the UK in the target population for the past 10 years as evidenced from the data in CPRD. The cohort of 428 patients treated with GP for sialorrhoea provided information on a population equivalent to 26,089 children age 3- 17 years covering 24,684 patient-years. Within this period, children received GP treatment for sialorrhoea for an equivalent of 435 patient-years. In total 1,797 treatment episodes occurred of which 1,565 (87.1%) lasted up to 6 months with a further 170 (9.5%) lasting from 7 to 18 months. The remaining 62 (3.4%) treatment episodes ranged from 19 to 92 months. AEs were related to the known anticholinergic effects and the

incidence of AEs decreased with increasing treatment duration. No additional repeat use non-clinical data would alter the safety conclusions from the available clinical information.

**Reproductive / developmental toxicity**

According to the Guideline on the non-clinical documentation for mixed marketing authorization applications, CPMP/SWP/799/95, 2005, investigations regarding fertility and general reproductive performance are generally not necessary unless there is cause for concern. Investigations of embryo-foetal toxicity and peri/post-natal development are not necessary if sufficient data from exposures in pregnant women and neonates are available or if the medicinal product is not intended for use in women of child-bearing potential or during pregnancy and lactation.

Glycopyrronium was not teratogenic in rats and rabbits. In preclinical studies investigating effects on fertility, conflicting results were obtained, but no clear and reproducible effect was observed. Excretion of glycopyrronium in milk was reported, and effects on postnatal development were observed in rats. In the currently proposed indication GP will be administered mainly to children, and no effects on reproduction are known from human experience. The data from the CPRD show no evidence that GP causes reproductive or developmental toxicity. AEs in CPRD showed that in the reproductive system there were 18 events in patients whilst being treated with GP out of a total of 63 events (m1.5.1. Appendix 1). Twelve separate events were recorded with no individual event occurring in the treated cohort on more than 3 occasions. There is no evidence of an effect of GP on the reproductive system in this patient population. Additional reproductive/developmental non-clinical studies would not alter the safety profile of GP nor change the contraindication in pregnancy and breast feeding. The Applicant proposes that the label will caution women of child bearing potential to take appropriate contraceptive precautions and warns that glycopyrronium should not be used in pregnant or lactating women.

**Genotoxicity and carcinogenicity**

From the available data in the published literature, GP was not mutagenic and not clastogenic in genotoxicity studies and was also not carcinogenic in carcinogenicity studies in rats and mice (Module 2.4).

The potential for carcinogenic effects was examined in the CPRD. The SOC Neoplasm showed 71 events in the full cohort of which 19 occurred during the GP treatment window. There were no AEs relating to a carcinogenic potential. Comparing the AEs in this SOC, within the GP treatment window compared to the full cohort shows the majority to be skin papilloma (15/58) [mainly warts and verrucae], followed by melanocytic naevus (3/13) [moles] and lipoma (1/3). There is no evidence of a carcinogenic potential of GP in this patient population. As such, no additional information that would alter clinical practice would be gained from preforming non-clinical genotoxicity or carcinogenicity studies.

**Extrapolation of safety margins and toxicokinetic exposure**

In repeated dose toxicity studies with oral and inhalation drug administration in mice, rats, and dogs, mainly an exaggerated pharmacodynamic activity was seen at high dose levels but no clear toxic effects outside of those associated with the PF activity were seen on any organ or tissue. The lowest NOAEL with inhalation was determined in a study in dogs with daily drug inhalation for 39 weeks at 0.02 mg/kg bw. The lowest NOAEL with oral drug administration was determined in mice at 30 mg/kg bw, although administered for 7 days only. As drug absorption from the gastrointestinal tract is low, and local effects in the lung were observed upon inhalation, the NOAEL from oral drug administration appears more relevant. The dose level of 30 mg/kg bw in the mouse corresponds to a human equivalent dose of 30 mg/kg / 12.3 = 2.44 mg/kg bw.

In children, the proposed starting dose is 0.02 mg/kg, three times a day, to be increased according to the schedule up to a maximum of 0.08 mg/kg (2.4 mg) three times a day, i.e. 7.2 mg/day or 0.24 mg/kg per day. Individual titration of doses is a critical aspect of administration since the margin between desirable effects and exaggerated pharmacology is small. The safety margin between the safe human equivalent dose calculated from the NOAEL with oral administration to mice of 2.44 mg/kg bw and the maximum intended dose in children can be calculated at 2.44 mg/kg bw / 0.24 mg/kg bw = 10.17. A safety margin of 10 is generally recognized as safe, and therefore with a safety margin of 10.17, the therapeutic use of glycopyrronium as recommended in the intended indication is not expected to be associated with any unexpected risk to human health.

Doses are not relevant per se but rather the resultant drug exposure (expressed as area under the plasma concentration-time curve, AUC), with the relationship between dose and AUC being primarily driven by clearance (AUC = dose/clearance). In this sense, the AUC obtained in adults and children of different body weights after administration of glycopyrronium bromide at the same dosing regimen (i.e., ~0.08 mg/kg three times a day, according to the dosing schedule proposed for Sialanar) was very similar (as depicted in the figure below) thus supporting the safety of the intended dosing regimen in both adults and children ≥3 years.

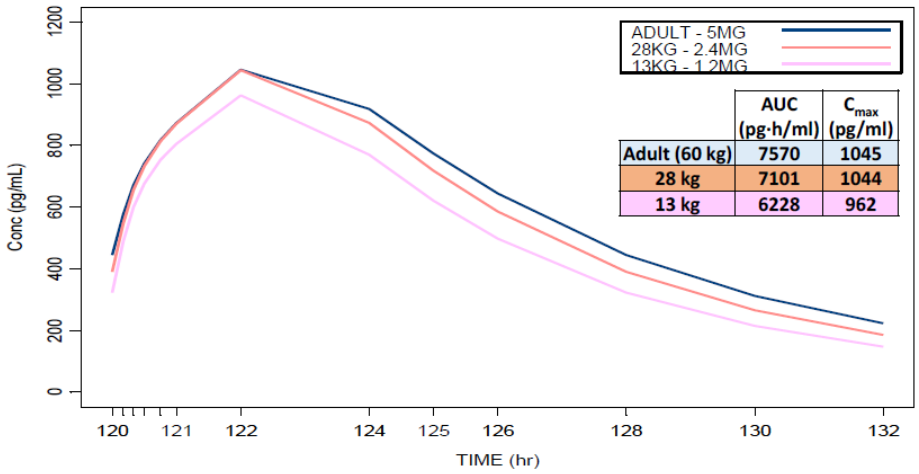



**Figure** Comparison of steady-state plasma glycopyrrolate levels
Comparison of steady-state plasma glycopyrrolate levels (means and 95% prediction intervals, upper panel; means, lower panel) simulated for Sialanar after repeated dosing (i.e., at Day 5 of treatment) with ~0.08 mg/kg three times daily in virtual populations (N=100 each) of children with 13 kg body weight (~3 years of age), 28 kg (~10 years of age) and adults (60 kg).

*Note: For clarity, only the last dose is shown, with the corresponding mean AUC and Cmax values for each population provided in the insert.*

Simulations (shown in the figure above) were performed using the compartmental PK parameters estimated in adults from the model developed by the applicant using data of study PRO/GLY/001, in conjunction with allometric extrapolation of clearance and volume of distribution to children of different body weights (m5.3.3.5). The data presented above and the extensive clinical efficacy and safety package provide sufficient evidence for the safe and effective use of GP in the target population. Additional non-clinical data on extrapolation of safety margins and toxicokinetic exposure would alter the clinical profile or use of GP.

## *Ground #3*

- A marketing authorisation application submitted under Article 10a of Directive 2001/83/EC must demonstrate that the use of the substance in the relevant indication has been in well-established medicinal use for at least 10 years in the European Union, with a recognised efficacy and an acceptable level of safety. The lack of sufficient and reliable qualitative and quantitative data and subsequent resulting uncertainties do not allow to establish that glycopyrronium bromide has been used in the European Union for the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders with an acceptable level of safety. The application falls therefore short of demonstrating that the requirements of Article 10a of Directive 2001/83/EC are fulfilled;

## Applicant's grounds for re-examination: Point 3

The CHMP considers that the lack of sufficient and reliable qualitative and quantitative data and subsequent resulting uncertainties do not allow establishment that GP has been used in the European Union for the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 to <18 years with neurological disorders due to a lack of information to support an acceptable level of safety. The application falls therefore short of demonstrating that the requirements of Article 10a of Directive 2001/83/EC are fulfilled.

The Applicant has provided adequate qualitative and quantitative data to confirm the well established medicinal use of GP in the target population for the target indication for more than 10 years in at least one EU country (m1.5.1) which confirms:
• The regular use of GP for the treatment of sialorrhoea for over 10 years in at least one EU country,
• The extent to which GP has been used in clinical practice,
• The extent of GP use on a geographical basis,
• The extent to which the use of GP has been monitored by pharmacovigilance or other methods,
• The degree of scientific interest and coherence of assessments in the use of GP,
• The efficacy and safety profile of GP in the target population for the target indication, and
• The efficacy and safety of GP within the EU.

The above information has been accepted by CHMP with the exception of the evidence to justify an acceptable level of safety. The above discussions on Point 1 and the comprehensive evidence presented in m2.5 fully justify the position that GP has an acceptable level of safety in the target population. The specific issues of chronic use of Sialanar in the paediatric population affected by the underlying conditions, with particular emphasis on the risks of cardiovascular effects, developmental effects, urinary retention and CNS effects have been examined, as well as the inclusion of data on differences in AE profiles depending on the age of the child, plus the risks associated with pneumonia. Data from the clinical trials and information extracted from the extensive real-life clinical use database, CPRD provides conclusive evidence that sufficient information is available for all points of concern regarding the use of GP in the target population. GP is dosed by slow titration, starting with a low dose based on body weight and increasing over several weeks to balance efficacy with side effects and tolerability.

As such, the application meets all of the requirements of Article 10a of Directive 2001/83/EC.

## *Ground #4*

- Having considered above the safety profile, it has also not been demonstrated that Sialanar is associated with any improvement in the quality of life in the claimed indication.

## Applicant's grounds for re-examination: Point 4

The CHMP do not consider that Sialanar is associated with any improvement in the quality of life in the claimed indication based on their view of the outstanding safety issues.

Use of GP for the treatment of sialorrhoea is based on its pharmacodynamic effect of drying secretions. Module 2.5.4 contains detailed analysis of the data supporting the efficacy of GP in the target population. Six published studies include data on the efficacy of GP in the treatment of sialorrhoea in children with neurological disorders (Parr, 2016, Zeller, 2012a; Zeller, 2012b; Meir, 2000; Blasco, 1996; Stern, 1997), which provide the basis for its clinical use in EU for over 10 years. The majority of the evidence supporting the efficacy of GP in sialorrhoea comes from the three pivotal studies (2 being 8-week, placebo controlled and one large open safety study). The efficacy of GP in long-term use was demonstrated in a 24 week open-label study by Zeller et al, 2012b, comprising a 4-week dose titration phase followed by a 20-week maintenance period at the individualized dose.

In addition, information is available from a recently completed 12 week trial conducted in the UK, comparing the efficacy and safety of GP against hyoscine for the treatment of sialorrhoea in the target population (Parr, 2016). Children age 3-15 years who had never received medication to treat drooling were recruited from 15 UK centres and randomised to hyoscine or glycopyrronium; stratification was by centre and drooling severity. Dose adjustment and side effect monitoring were undertaken weekly by the trial team over 4 weeks to identify the most effective dose for each child in the context of any side effects. Primary outcome data were gathered with the standardised Drooling Impact Scale (DIS) at 4 weeks by a researcher blind to treatment group status. Follow up continued to 12 weeks.

Ninety children (median age 4.9 years) were randomised (49 hyoscine and 41 glycopyrronium). Of these, 48 children started hyoscine treatment, and 38 started glycopyrronium. By 4 weeks, 35/48 children (73%) remained on hyoscine and 33/38 (87%) on glycopyrronium; the remaining children had stopped trial medication due to side effects. By 12 weeks, 26/48 children (54%) remained on hyoscine and 31/38 (82%) on glycopyrronium. At 4 weeks there was no significant difference in DIS scores between the treatment groups suggesting both medications were equally effective at the maximum tolerated dose. However, by 4 and 12 weeks hyoscine was associated with more problematic side effects than glycopyrronium and parents were more likely to withdraw hyoscine treatment.

Therefore, all clinical studies conducted in the target population concluded that GP was an efficacious drug with an acceptable benefit-risk profile when dosed to clinical effect, balanced with side effects, over a number of weeks.

However, it is important to know whether improving drooling will have a positive impact a patient's Quality of Life (QOL). Drooling itself has a substantial impact on utility (and therefore on overall health related quality of life). As such, it follows that reducing drooling, for example with GP, would have a positive impact on the patient's QOL. The effect of drooling on QoL has been conducted in patients with cerebral palsy. Mapping this data has allowed an estimation of utility values for drooling in cerebral palsy (QOL Mapping), provided as m2.5 Appendix 1. An improvement in drooling through treatment with GP would equate to an improvement in QOL in patients with cerebral palsy. Whilst there are several limitations that could decrease the validity of the application of the mapping algorithm the analysis of the difference in QOL in paediatric patients with cerebral palsy is significant between patients who drool and those who never drool.

The safety data presented above and in m2.5 confirms the expected safety profile for GP whether in published trials or in the analysis of data from CPRD. Evidence shows increased AEs with GP treatment, which

are dose related and, as evidenced in the DRI study, led to discontinuation of treatment in just 18% of case versus 45% in patients on hyoscine. It is also clear from the results of the DRI study that parents are able to recognize side effects, modify dose or withdraw treatment as necessary, thereby ensuring that any improvement in the child's QOL is not compromised by the presence of adverse events.

There is no evidence to suggest GP causes any new AEs, beyond those known with anticholinergic drugs, and seen in both clinical trials and the CPRD. The slow dose titration, based on body weight, and the flexibility afforded with a liquid presentation, delivered through an oral dosing syringe, allows AEs to be easily managed through dose reduction or treatment withdrawal if required. As shown in the DRI study, parents/carers are able to recognize and mange AEs through dose reduction or withdrawal as required. As such, the improvement in QOL provided by effective treatment is not compromised by adverse events since these can be effectively managed through dose adjustment. The fact that many patients remain on treatment for several months and in some cases years supports the positive benefit : risk ratio for Sialanar in the treatment of chronic drooling in children with neurological disorders.

**Applicant's Overall Summary of Grounds for Re-Examination**

Uncertainties about safety in relation to chronic use, age, CV system, CNS including behaviour and neurodevelopment, urinary retention and pneumonia have been discussed in detail above and in m2.5. The significant adverse events of urinary retention, constipation and pneumonia are associated with use of GP, as evidenced by clinical trials and CPRD data. These events have the potential for significant clinical implications and evidence from CPRD suggests that treatment discontinuation is the current clinical practice. The Applicant has included urinary retention, constipation and pneumonia in the SmPC as adverse events requiring treatment discontinuation should they occur.

There is no information to suggest an effect of GP on neurodevelopment or growth (height and weight). Cerebral palsy and other neurodevelopmental disabilities are known to be associated with reduced growth and difficulty in feeding often means the children are underweight for their age. The SmPC includes a statement that the effects on growth and neurodevelopment are unknown and no studies have been conducted to specifically address such an effect.

The non-clinical data to address repeat-use toxicology, reproductive/developmental toxicology, genotoxicity and carcinogenicity and extrapolation of safety margins to the proposed population have been discussed based on both non-clinical and clinical evidence. The data provides sufficient assurance on each of these points, given the extent of clinical use and the detailed evidence available from CPRD. New nonclinical data would not provide evidence to alter any of the paediatric safety information or the proposed labelling.

It is important to ensure that any known improvement in QOL, resulting from effective reduction of drooling with GP, is not offset by the presence of detrimental adverse effects. The safety data presented in the application confirms the expected safety profile for GP both in published trials and in the analysis of data from CPRD. Evidence shows increased AEs with GP treatment, which are dose related. However, as evidenced in the DRI study, AEs lead to discontinuation of treatment in just 18% of case versus 45% in patients on hyoscine showing they can be effectively managed through dose adjustment or withdrawal as necessary. Therefore, improvement in QOL through effective treatment would not be overshadowed by adverse events, supporting the overall positive benefit : risk ratio in this chronically disabled population. In addition, it is clear that parents/carers are well able to recognise and manage AEs and maintain adequate reduction in drooling for an improved QOL.

In conclusion, the safety of Sialanar is sufficiently characterized and the benefits of treatment outweigh the safety risks for the symptomatic treatment of sialorrhoea (chronic pathological drooling) in children and

adolescents aged 3 to <18 years with neurological disorders. The Applicant has justified a favourable overall benefit/risk balance with sufficient safety evidence to allow the granting of the marketing authorization for Sialanar.

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc expert Group inviting the experts to provide their views on specific questions based on the CHMP grounds for refusal, taking into account the applicant's response.

**Report from the ad hoc expert group**

**1. Please discuss the negative consequences associated with excessive drooling in children and adolescents with neurological conditions with respect to health and quality of life.**

**a. How is the condition handled in clinical practice? If medical treatment is given, is the treatment chronic or intermittent?**

Different treatment approaches to pathological drooling exist varying from country to country and depending on the severity of the condition. In the UK and in Belgium, Glycopyrronium (or Hyoscine patches) are in regular use particularly in the palliative care setting given continuously in patients with progressive disease and at the end of life and in children with cerebral palsy and other severe neurological problems. Whereas Hyoscine patches carry the advantage of easier application, oral glycopyrronium can be titrated more easily. Together with Botulinumtoxin injections physicians choose from this armamentarium depending on treatment response of the individual patient.

On the other hand, in Sweden, speech therapy is the preferred treatment approach and drug treatment like Scopolamin or Botulinumtoxin injections are seldom used (Atropin in the palliative care setting). In the Netherlands treatment is started with speech therapy/awareness as the first step, followed by Botulinumtoxin injections. Glycopyrronium are given intermittently / short term in case Botulinumtoxin injections are not feasible.

As a whole, treatment duration depends on the patient conditions. In palliative care it is rather long term continuous, in other situations it may be more short term/intermittent.

The experts noted that none of these options have a license for such use and the diversity is also driven by what is locally available. It was generally agreed that Glycopyrronium should only be used in clearly severe cases of drooling and the treatment closely monitored by specialists in the field.

**b. What are the most serious consequences for the patients and care givers associated with excessive drooling?**

Aspiration was considered as one of the most important consequences of drooling. In severely affected patients the control of potential reflux in children heavily choking was considered critical to alleviate distress. Other raised consequences were sore skin and dehydration in patients with Rett Syndrome. In less affected patients also psychosocial concerns like embarrassment and lower self-esteem play a role. Overall the experts highlighted that excessive drooling as seen in severe cases is significantly impacting the patients and treatment is an important element of patient care.

**c. Is there an unmet medical need that could potentially be fulfilled by glycopyrronium bromide?**

The experts considered that for the treatment of severe drooling, all available treatment options have their limitations. None of the alternatives is approved. Furthermore, the Botulinumtoxin injections are very

dependent on the expertise of the treating doctor, Hyoscine patches do not allow sufficient dose titration and radiotherapy can lead to overtreatment. Crushed tablets of Glycopyrronium are broadly used in clinical practise with uncertain bioavailability. An age adapted oral formulation with stable bioavailability of Glycopyrronium would allow dose titration which would help to individualize the treatment in particular for severely affected patients with severe oropharyngeal dysphagia who are often treated with numerous drugs. In the United Kingdom Glycopyrronium is used as part of the treatment protocol of severe siallorhea in terminal ill patients.

**d. Please reflect on your potential clinical experience with anticholinergics, including glycopyrronium bromide, in the treatment of children and adolescents with neurological conditions, with respect to impact on QoL, efficacy and safety, duration of treatment etc.**

The experts considered that in severe drooling where the patient is choking and may be at risk of aspiration and dehydration, the impact on QoL of an effective therapy can easily be assumed. The duration of treatment in severe progressive disease is continuous but depends on the response of the patient. To get severe consequences of drooling under control is an interdisciplinary approach including also pulmonologists.

The place in therapy was not seen within a light or moderately affected patient population due to the side effects and the use of speech therapy as first line treatment.

It was further emphasized that expert prescription would be crucial taking into consideration comorbidities and co-medication of these patients. Constipation is commonly seen in these patients due to immobility and might become more severe under Glycopyrronium.

2. **From a pharmacological point of view, the adverse event profile of glycopyrronium bromide could be considered to be predictable (potent M3 blocker, but also with affinity at all five human muscarinic acetylcholine (ACh) receptor subtypes). However, literature data confirming the safety profile in paediatric and chronical clinical use is sparse.**

   **a. Which are in your view, the most serious/relevant adverse events that could be expected in the target population in clinical practice (e.g urine retention, dry mouth with secondary risk for caries, pneumonia, obstipation, CNS effects)?**

Over drying was emphasized as one of the most serious concerns as it leads to thick mucus which may lead to pneumonia. Furthermore, constipation is common in this less mobile patient population and can get more severe. Also worsening of balance problems were observed in clinical practise. The risk of caries was particularly emphasized and risk minimisation measure should strongly address this issue. The risk of urinary retention was acknowledged but rather seen as a result of too quick up titration. Urinary retention was perceived manageable for a drug with predictable bioavailability with regular check-ups and adequate information to the prescriber about dose titration. Furthermore, the carer should be informed not to change the dose without expert advice.

The effects on CNS of concomitant medication rather than Glycopyrronium in severely affected patients may be more pronounced. A possible additional effect of Glycopyrronium on CNS might be negligible in the context of severe disease.

Less severe affected patient with pre-existing ataxia should certainly not be considered for treatment with Glycopyrronium.

**b. Please discuss the possibility to identify these adverse events in children with neurological conditions. Is there a risk that a too high dose of glycopyrronium bromide may be given since adverse events may not be detected?**

Severely affected patients are mostly also handicapped in their ability to communicate due to their neurological condition. However the experts considered that parents / carers of these patients are in general very skilful to interpret their non-verbal communication and to raise potential side effects to the treating physician. Careful titration of the right dose by the treating physician together with robust guidance on the identification and management of side effects may minimize this risk.

**c. Please discuss to what extent these are manageable AEs and what additional risk minimization measures could be implemented to ensure a safer use**

Parents of affected patients were considered to actively seek information about the well-being of their children. Therefore, easily understandable and readable educational material should be available for them and the dose should not be increased by the carers without specialist consultation. In addition, dedicated material for adolescents would be needed. In particular, as long term safety information was considered scarce there would be a need to inform patients / carers how to interpret indirect symptoms and record relevant information (e.g. urine diary), as well as a regular check at close time intervals by the treating specialist.

**d. Please discuss if additional data would be needed to characterize the safety profile in the proposed target population**

Deficiencies in robust long-term data and the long term benefit risk were acknowledged by the experts but needs to be seen in the context of the severity of the disease. Reassurance that patients are given the most appropriate dose with the recommended titration scheme would make sense which may be covered by a drug utilisation study.

3. **Are there differences on how drooling affects Quality of life in different age groups of the target population? Considering different degrees of neurological impairment would it be easier for older children and adolescents (appr.>12 years) to express symptoms from side effects of an anti-cholinergic acting drug than for younger children i.e. could benefit risk for Sialanar be different for different age groups?**

The experts emphasised the current limitation of the use to severe patients and confirmed that in clinical practice identification of side effects in this population should be feasible. Severe drooling was considered sufficiently defined as understandable term for the prescriber. Whereas older paediatric patients may rather be treated with Botulinumtoxin injections, the age range was seen of rather negligible importance by the experts for the benefit from the treatment and quality of life. More importantly impacting on the benefit is the severity of the drooling. The age cut of 3 years was considered appropriate for a label as reflecting the population where data is available, however reflecting clinical practise in the UK, it might make sense not to contraindicate the treatment even in younger children as in very particular circumstances, such as at the end of life, there might be a use.

***Overall conclusion on grounds for re-examination***

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group.

## *Ground #1*

Muscarinic receptors are widely distributed throughout the human body and mediate distinct physiological functions according to location and receptor subtype (see Caulfield & Birdsall, 1998). Five distinct muscarinic receptor subtypes (M1–M5) are known to exist, although the exact location and functional role of all these subtypes has to date not been fully elucidated (Abrams et al, British J of Pharmacology, 2006). Glycopyrronium bromide (GP) is a potent M3 blocker. Salivation is primarily mediated by M3 receptor. However, GP has affinity at all five human muscarinic acetylcholine (ACh) receptor subtypes (Ki = 0.15 – 2.0 nM) in order M1 > M3 > M2/M4 > M5. GP is 2-4 times more selective for the M3 and M1 subtypes than M2 (Bird et al. 2011). This has implication for the effects and adverse events of anti cholinergic drugs. These side effects may be a clinical disadvantage when using drugs with anti-cholinergic effects and especially in long-time treatment.

The frequency of adverse anticholinergic effect are ranging between 10-40% in the data presented by the Applicant and for most of the events difference from placebo was seen in the placebo controlled studies (Zeller 2012a and Mier 2000). The adverse events are dose dependent. The Applicant proposes a dose titration table to establish the lowest effective individual dose and with a careful assessment of side effects which is reasonable.

The therapeutic effect of GP is easily assessed by the caregiver. However, when it comes to adverse events such as, dry mouth with risk for caries and urinary retention, the symptoms may be difficult for the caregiver to identify when the patient has limited ability to communicate. Urinary retention can predispose for urinary infections and also reflux leading to tubular atrophy and renal injury.

The concerns of the CHMP were particularly with regards to cardiovascular effect, CNS effects, urinary retention and developmental effects. In addition as a result of the pharmacological effect there is a high risk of dry mouth with a secondary risk for caries.

Cardiovascular effects

The plasma concentration of GP required for effective vagolysis has been determined to be at least 10 µg/L. In studies in children by Rautokorpi et al, 1994 and Rautokorpi et al, 1998 plasma concentrations following a 5 µg/kg i.v. dose of GP only briefly exceeded this concentration immediately following administration. In study PRO/GLY/001, the maximum plasma concentration after 2 mg (~0.03 mg/kg) of Sialanar in adult volunteers occurred between 3 and 7 hours post dose, reaching a maxima of ~1000 pg/mL (i.e. 1 µg/L). The highest dose of Sialanar(0.1 mg/kg) in the Applicant's proposed posology is 3.3 fold higher than the average dose (in mg/kg terms) tested in PRO/GLY/001. It is therefore conceivable, given the variability in exposure to GP after oral administration, that some paediatric patients at the highest dose(s) may briefly attain a plasma concentration of GP sufficient to cause a vagolytic effect. This observations were confirmed by the number of occurrences of cardiac events which were extremely low in the CPRD . No significant effects of HR were seen in the pediatric data presented by the applicant. In addition, no effects were seen on blood pressure and the experts having experience of GP use, did not recognized CV effects as a common adverse effect in this patient population. Considering the expert opinions, the available data mentioned above this is considered to be reassuring. The CHMP considers therefore that the remaining potential risk is acceptable considering the clinical benefit which is more relevant for severely affected patients comprised in the amended indication. The SmPC informs about cardiac effects and outlines that effects on the cardiovascular system should be considered when assessing tolerability and additionally robust educational material was established (see also conclusion on ground 1 below) which is considered to be sufficient in this setting.

Central nervous system

In the brain are mainly M1 receptors. The Applicant states that GP passes the BBB in very limited amount except in situations where the BBB has been compromised e.g. by a shunt infection. However, there are several situations where the BBB becomes 'leaky' following damage (e.g. under conditions of stress, advanced age or presence of comorbid conditions such as diabetes or multiple sclerosis) (Abrams et al, British J of Pharmacology, 2006). The grade of passage over the BBB is also affected by the dose and at long-term treatment a certain passage cannot be excluded for all patients. In the study of Mier there was a higher frequency of AEs related to CNS (23%) in the GP group compared to placebo and the Applicant points to that the dose in the Mier study was higher. Still, this raises concern that some children treated have a more pronounced risk of transfer of GP into CNS. The main concern of the CHMP was that in the case of CNS adverse effects these may be difficult to assess for the caregiver and depending on the neurological disease with fluctuations of alertness can be difficult to distinguish from side effects of the medication.

The ad hoc experts acknowledged that potential effect on CNS may be seen with the use of GP, but based on their experience this may not be a serious problem in severely affected patients who are taking in general multiple medications with CNS effects. This was taken into consideration by the CHMP together with the expert's view that caregivers / parents of these patients can be considered in general highly skillful to detect changes in the behavior of their children. Considering the narrower indication (severely affected patients) and the particular clinical benefit of these patients available data with respect to potential risk of CNS effect was considered as sufficient by the CHMP and a potential risk was considered acceptable with the warning included into the SmPC on CNS adverse effects and the established risk minimization measures.

Concerning neurological development including growth the Applicant points to that there are no evident reports of AEs during the ten years that GP has been used in the UK. Furthermore, the CPRD does not give any indication of effects on neurodevelopment. Even though the CHMP recognizes that this data, due to its nature, must be interpreted with care. However considering that the indication was restricted to short-term intermittent use and the exposure will be minimized also in case of repeated treatment this issue can be considered solved.

Other effects

Another serious side effect is pneumonia and the data from Zeller 2012(b) suggests a causal relationship with GP, this was acknowledged by the Applicant and advice is added to the SmPC and the educational material that, should it occur, the treatment should be discontinued. The experts raised that inappropriate dosing of GP leads to thick mucus and pneumonia and that this risk can be considered manageable with careful titration. Obstipation is a further side effect that may be severe in this setting of patients because this may also be a result of the low degree of physical activity in these patients. However, based on the deliberations of the experts this side effect is considered sufficiently detectable by a caregiver trained with adequate educational material if advised to be attentive to this risk.

Based on the expert feedback the CHMP considers both, pneumonia (via over drying) and obstipation to be manageable by the trained and experience caregiver and prescriber as they are detectable and mostly results of inappropriate titration. This key problem is now sufficiently addressed by educational material and the planned DUS (as outlined in the RMP). Taking all this into consideration, the CHMP concluded that the submitted data referring to these adverse events is sufficient for an approval in the new target population.

Urinary retention was reported with an incidence of 13-15% with GP in randomized controlled clinical studies whereas not occurring in the placebo arm and there was no information provided on the severity of the episodes of urinary retention nor if it was associated with an increased incidence of urinary tract infections.

This risk of urinary retention was acknowledged by the experts even though not commonly seen in the treated patients in clinical practice. The experts considered urinary retention sufficiently detectable by the caregivers (e.g. by urine diary) and as manageable with careful titration of the drug by the treating physician together with robust guidance on the identification and management of side effects. The CHMP considers that taking into consideration the expert prescription, the caregivers which were seen as in general very skillful by the ad hoc experts in detecting side effects, the recommendations given in the SmPC and in the educational material on careful titration and recommended action if side effects occur as sufficient to balance the risk of urinary retention. An age appropriate formulation of GP such as Sialanar may also facilitate titration as outlined by the expert. Furthermore the implemented DUS addresses further the underlying problem of inadequate titration which was stressed by the ad hoc expert. Together with the implemented short-term intermittent use and recommendations in the SmPC on considering carefully the benefit risk of the patient if treatment is repeated sufficient assurance is given on the control of this risk.

Dry mouth is probably an inevitable side effect of GP as this is the effect that the treatment is aiming for. It is known that dry mouth is a severe risk factor for caries and a high level of mouth hygiene is necessary. As these patients need general anesthesia in relation to dental visits robust educational material for the caregivers is put in place as emphasized by the experts which is considered to control sufficiently for this risk.

Chronic use

The data submitted may support short-term treatment but there are limited long term data (24 weeks and controlled data only 12 weeks). Since the substance is well known it is reasonable to believe that the long term adverse events relating to the anticholinergic effect are similar to those seen in more short term. However, other potential long term safety concerns are less well characterized (see ground 2). For this reasons the CHMP considers that the treatment should be applied only short term as outlined in the SmPC.

Deficiencies in robust long-term data and the long term benefit risk were also acknowledged by the experts who emphasized however that needs should be seen in the context of the severity of the disease. Reassurance that patients are given the most appropriate dose with the recommended titration scheme would make sense which may be covered by a drug utilisation study. The experts further emphasized that expert prescription would be crucial taking into consideration comorbidities and co-medication of these patients and that a definite restriction of the duration of use should be avoided since treatment is highly individualized in clinical practice.

Taken together the submitted data and the experts advice the CHMP considered that the safety profile remains insufficiently characterized for chronic use in all grades of severity of siallorhea and the application of the treatment was restricted to short -term intermittent use in severe cases. The safety characterization in this setting can be considered acceptable considering the submitted data and the statements in the SmPC on keeping total treatment duration as short as possible. However in a palliative care setting where the duration of treatment is limited due to the terminal disease state different benefit risk considerations apply and a continuous treatment can be considered by the treating expert prescriber who carefully monitors the patient as outlined in the SmPC.

**Conclusion on Ground 1** Taking into consideration the side effect profile of Sialanar which is typical for the anticholinergic action of the drug and the expert advice received the CHMP considers that careful titration of the dose by the treating physician together with robust guidance on the identification and management of side effects can minimize the expected risks associated with the use of GP in severely affected patient. The following considerations play a critical role to be confident that the safety of these patients can be balanced and the safety profile be considered to be sufficiently characterized in the patients comprised by the

indication:

- The treatment is to be applied short term-intermittently only and the SmPC informs the treating physician that the treatment duration should be kept as short as possible which takes account the limited data in the long term setting. In the palliative care setting, more flexibility is foreseen.

- The benefit of the patient to control drooling in the severely affected population can be considered highly clinically relevant as it reduces beside psychological consequences the risk of reflux and aspiration. In this situation a favorable impact on the QoL of the patients can be anticipated.

- The most significant side effects such as urinary retention, constipation, cardiovascular and CNS effects were considered by the ad hoc experts to be either a consequence of inadequate dosing and manageable with an appropriate titration schedule or acceptable in the context of severe siallorhea under control of an expert prescriber.

- Parents of affected patients were considered by the ad hoc expert group to be in general very skillful to interpret their non-verbal communication and eager to seek information about the well-being of their children. This adds certainty into the effectiveness of easily understandable and readable educational material which will be made available.

As outlined in the SmPC the dose should not be increased by the caregivers without specialist consultation and further assurance that the approved titration scheme will be applied will be given in a DUS as described in the RMP. Patients / caregivers will be informed how to interpret indirect symptoms and how to take appropriate actions such as stopping the treatment if relevant side effects occur. This is combined with close monitoring by the treating physician who is instructed by the SmPC to consider carefully the benefits and risks of the patient should treatment be needed repeated intermittently or longer term in the palliative care setting. Based on these considerations, adaptations of the label and in particular based on the input of the ad hoc experts the CHMP concludes that the safety in the patients comprised by the label is sufficiently characterized for granting a marketing authorization. The indication was adapted to severely affected patients and to short term intermittent use

**Point resolved**

### *Ground #2*

Reference to data from the Product Monograph of Seebri Breezhaler is not considered to be acceptable. Seebri Breezhaler was approved 28/09/2012 and the data is therefore still protected based on the 8 year of data exclusivity applied within the European Union (EMA Procedural advice for users of the centralized procedure for generic/hybrid applications. Doc. Ref. EMEA/CHMP/225411/2006 December 2005). The data generated for Seebri Breezhaler can thus not be taken into account when assessing the present MAA without a letter of access from the marketing authorization holder.

The three publications referred to (in addition to the monograph) are not considered to be sufficient to fully characterize reproductive toxicity, genotoxicity and carcinogenicity. Two of the publications are only short summaries, with only brief presentations of experimental details and results, and only the front page of the third publication, a book edited by Colin Dollery, has been submitted. (No assessment of the publication by Colin Dollery has therefore been made.)

CHMP's concern regarding repeat use toxicology and extrapolation of safety margins to the proposed population (chronic treatment of all severity grades of siallorhea) has not been resolved by the Applicant's response. Therefore and also based on safety considerations described in ground 1 above the treatment

duration was restricted to short term-intermittent use. The CHMP took also into consideration that the safety profile was considered by the ad hoc experts to be predictable and manageable with the applied dose titration scheme, educational material and monitoring of the benefit/risk balance of the medicinal product as discussed at ground 1. The publications referred to by the applicant contain no data regarding genotoxicity or carcinogenicity and only a very brief presentation of reproductive toxicity data from one study in rats (see table below which contain all data presented) and a statement that "careful examination of offspring born to drug-treated rats revealed no abnormalities attributed to drug administration". This was not considered to be sufficient for the claimed indication of chronic treatment of siallorhea in all grades of severity.

**Table 24**

SUMMARY OF REPRODUCTIVE PERFORMANCE OF RATS GIVEN GLYCOPYRROLATE

| Parameter | Control | | | Glycopyrrolate | | |
|---|---|---|---|---|---|---|
| | First litters | Second litters | Third litters | First litters | Second litters | Third litters |
| No. litters/group | 19/20 | 18/20 | 18/20 | 14/20 | 13/18 | 13/18 |
| No. stillbirths | 1 | 0 | 7 | 8 | 1 | 9 |
| Mean No. live young at birth | 11.2 | 10.7 | 12.1 | 7.7 | 8.8 | 8.0 |
| Lactation index* | 93 | 93 | 92 | 68 | 69 | 96 |
| Mean weight (g) | | | | | | |
| Birth | 6.0 | 6.2 | 6.0 | 6.1 | 6.0 | 6.2 |
| Weaning | 33.6 | 37.6 | 41.3 | 34.0 | 34.8 | 41.3 |

* No. pups weaned/No. pups alive at birth × 100.

The CHMP acknowledges however that clinical data from the CPRD do not show evidence that glycopyrronium causes reproductive or developmental toxicity and no evidence of a carcinogenic potential in this patient population. The presentations of the performed analysis of clinical data from the CPRD are very brief and not considered to be sufficient in order to make definite conclusions regarding possible reproductive or carcinogenic effects of glycopyrronium. No information regarding possible treatment of pregnant women is presented and it is also noted that the maximum length of treatment is stated to be below 8 years (92 month, with only 62 treatment episodes ranging from 19 to 92 month). Whereas concerns on reproductive and developmental toxicity can be considered sufficiently addressed in this patient population with the inclusion of a contraindication in pregnancy / breast feeding women, requiring contraception where applicable and outlining the sparse non clinical data in 5.3 of the SmPC the CPRD data alone and the information included in the SmPC on the absence of appropriate non-clinical tests alone cannot be considered to be a sufficient basis for conclusions regarding a possible carcinogenic potential of glycopyrronium or giving sufficient basis for the management of this risk. A carcinogenic potential of GP has not been reported within the therapeutic class. Nevertheless, in the absence of dedicated studies with Sialanar, this uncertainty remains acknowledged by the committee and control and reduction of exposure taking into consideration the individual patients profile is needed. This is now addressed in the SmPC by the short-term intermittent use and the monitoring of the benefit risk profile by the treating physician should repeated treatment be needed.

**Point resolved**

## *Ground #3*

The requirements described in Article 10a were discussed at length during the previous procedure and are summarised below:

It appears that the use of the substance in the European Union in the intended indication has been limited, except in the United Kingdom, where the Applicant provided the following evidence of use: It has been included in the British National Formulary for Children (BNFc) for the past 10 years; Direct evidence from prescription cost analysis (PCA) data for 15 years and feedback from individual prescribers to support its use for longer than 10 years within the UK in the claimed indication was submitted. In addition, the Applicant was able to show a considerably high number of prescriptions for drooling or related disorders, calculated from the UK database Clinical Practice Research Datalink (CPRD). Detailed information such as age, diagnoses, medical history and medication history were also provided. A total of 428 children from the CPRD database were identified as treated with GP for pathological drooling due to neurological disorders in the period 2006-2015.When taking into account the prevalence of the condition, the CHMP considered this evidence as sufficient to meet the quantitative requirements for well-established in the EU.
*In order to substantiate the scientific interest, t*he Applicant provided a comprehensive overview of the literature published world-wide over the past 23 years and 21 publications where identified, most of them non-European, or did not provide detailed information of GP. The Applicant also provided proof of two clinical studies conducted in the EU: a double-blind, randomised placebo-controlled study investigating an oral solution of glycopyrronium in children with hypersalivation associated with neurodevelopmental disability (ongoing in Slovakia and Czech Republic) and a single-blind study comparing an oral solution of glycopyrronium with a hyoscine cutaneous patch in drooling in children with neurodisability (performed in the UK). Whilst these studies are not yet available in the published literature and do not provide detailed safety and efficacy information, they provide valuable information on current clinical development of this active substance in the claimed indication. Overall, the submitted references above described were already considered sufficient evidence of scientific interest in the EU.

*Coherence of scientific assessments*
The Applicant provided an overview of the publications in which, overall, the reports are sufficiently consistent in outlining the effect of GP in pathological drooling in children, and therefore the CHMP considered that the coherence of the scientific assessments had been shown.

As a conclusion of the assessment of the above criteria, the CHMP was of the view that the Applicant provided sufficient evidence to establish that the elements related to the quantitative aspects of the use of the substance, the time over which the substance has been used, the degree of scientific interest in the use of the substance in the EU and the coherence of the scientific assessments are fulfilled. However, in the first round, the CHMP considered that there was insufficient evidence to consider that GP has been used in the EU with an acceptable level of safety in the claimed indication.

As outlined in the assessment of Ground 1#, long-term data are limited and although overall predictable based on the MoA, important uncertainties on the long term effects remain. Therefore the target population has been restricted to short term intermittent use in severely affected patients. Proof of an acceptable level of safety in this population has been addressed with ground 1 and 2. There is confirmed clinical use in severe Sialorrhoea. Most of the publications are for severe drooling and the well-established use in the restricted patient population can be agreed.
With regards to efficacy the Applicant summarized information from the pivotal submitted publications, supporting that children with severe drooling (as defined by the modified Teacher´s Drooling Scale) were included and also constituted the majority of the patients in the studies.

Zeller, 2012a was an 8 week placebo controlled study in patients with severe drooling (mTDS score of 6 or

higher, which defines a severe and profuse population). The responder rate was significantly higher for glycopyrronium treated patients (14/19; 73.7%) compared to placebo (3/17; 17.6%) p=0.0011. At 8 weeks the mean improvements in mTDS score at week 8 were 3.94 points for GP compared to 0.71 for placebo (p<0.0001).

Mier, 2000 conducted an 8 week placebo controlled study in children with severe and profuse drooling, as reflected in the mean baseline drooling scores or 7.52 for glycopyrronium and 7.44 for placebo. Scores improved over the 8-week study from 7.52 to a max mean score of 1.85 (dry, never drools and mild drooling) in the glycopyrronium group and from 7.44 to 6.33 in the placebo group. Although data were not dicomised by severity of the condition at baseline, the study results are considered relevant to the restricted population as this was well represented. Zeller 2012b5 conducted an open-label 24 week safety study which recorded efficacy from baseline. Of the study population, 68.2% of children had baseline drooling severe or profuse in nature. A moderate severity was recorded in 32.1% of children. Results show that the treatment is most effective in the profuse (31.6% to 2.3%) and severe (36.6% to 8.3%) populations. By the end of the study the number of children with profuse and severe drooling decreased from 31.6% to 2.3% and 36.6% to 8.3%, respectively. The improvement in the moderate population was less, 32.1% to 25.6%. Parr 20166, conducted a 12 week comparator-controlled (hyoscine) study in which children had moderate or severe drooling. The breakdown of the drooling scores is not currently available. Glycopyrronium was found to have equivalent efficacy to hyoscine over the 12-week study in terms of drooling impact score.

The overall benefit of treatment in these patients should also take into account prevention of potential serious risks associated with severe drooling and the secondary predictable improvement in QoL. Therefore, efficacy is considered well substantiated also in the subset of patients with severe drooling.

Safety was not presented by severity, but since patients with severe drooling constitute an important portion of the main studies, results are considered representative and supportive of the safety in the subgroup of patients. Thus, the submitted data is considered as relevant also for the children with severe drooling.

**Point resolved**

### *Ground #4*

Data indicate an effect on QoL as 100% of caregivers in the Zeller 2012a study assessed that the treatment was worthwhile as compared with placebo 56.3%.

Even though there is very limited published data with respect to improvement of QoL associated with GP treatment, the experts at the SAG meeting confirmed that excessive drooling as seen in severe cases is significantly impacting the patients and treatment is an important element of patient care. Aspiration was considered as one of the most important consequences of severe drooling. In severely affected patients the control of potential reflux in children heavily choking was considered critical to alleviate distress.

Treatment approaches to pathological drooling vary from country to country and depend on the severity of the condition. In the UK and in Belgium, GP (or Hyoscine patches) are in regular use particularly in the palliative care setting given continuously in patients with progressive disease and at the end of life. Whereas Hyoscine patches carry the advantage of easier application, oral GP can be titrated more easily. Together with Botulinum toxin injections physicians choose from this armamentarium depending on treatment response of the individual patient.

An age adapted oral formulation of GP would allow dose titration which would help to individualize the treatment in particular for severely affected patients who are often treated with numerous drugs.

Considering the indication being adapted to severe cases where the treatment of sialorrhoea can be used to alleviate distress an improvement of QoL can be expected.

**Point resolved**

## *5.1. Risk Management Plan*

The CHMP considered that the risk management plan version 1.5 could be acceptable if the applicant implemented changes to the educational materials and submitted a synopsis for a drug utilisation study. In addition, changes relating to the overall quality of the content of the document were made.

The applicant implemented most of the changes in the RMP as requested by CHMP in version 1.9. However, the RMP could benefit from further improvement and, therefore, the company is requested to submit a new version of the RMP two months after Commission Decision for a stand-alone assessment.

***Safety concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Off label treatment of children with mild to moderate sialorrhoea.<br>• Treatment of patients with severe renal impairment (eGFR <30 ml/min/1.73m$^2$), including those with end-stage renal disease requiring dialysis<br>• Anticholinergic effects<br>o Constipation<br>o Urinary retention<br>o Pneumonia<br>o Risk of overheating<br>o CNS effects<br>o Overdose<br>• Unintentional overdose due to 8ml syringe<br>• Interactions with other medicinal products |
| Important potential risks | • Cardiac disorders<br>• Dental caries<br>• CNS effects |
| Missing information | • Safety in long-term use, beyond 24 weeks has not been established<br>• Use in patients below the age of 3 years<br>• Use in patients with compromised blood brain barrier |

***Pharmacovigilance plan***

| **Study / activity Type, title and category (1-3)** | **Objectives** | **Safety concerns addressed** | **Status (planned, started)** | **Date for submission of interim or final reports (planned or actual)** |
|---|---|---|---|---|
| Drug Utilisation Study (DUS) for the characterisation of the use of Sialanar (glycopyrronium oral liquid 0.32mg/ml) in the treatment of severe chronic pathological drooling (sialorrhoea) and concordance with the approved labelling. | The primary objective is to monitor and assess effectiveness of additional risk minimisation measures for side effects occurred while on Sialanar treatment.<br><br>Incidence of patients receiving follow up consultations (in person or by telephone) for medication review initiated by the carer, included the reasons the consultation (e.g. side effects in between the stated 3 monthly interval will be assessed, other). | Incidence of patients experiencing adverse events, including anticholinergic side effects, brought to the attention of the treating physician/prescriber by the carer in between the stated 3 months (+/-2 weeks) routine consultation time interval.<br><br>Incidence of patients receiving follow up consultations (in person or by telephone) for medication review at 3 monthly intervals (+/- 2 weeks)) | Planned | Planned<br><br>Start up report including cohort accrual estimate, ethics approval plan etc (TBC July 2017)<br><br>6 month progress report including recruitment progress (TBC Jan 2018)<br><br>Interim report half way through study. Data lock 18 months after study start (TBC Jan 2019), report 3 months later (TBC Apr 2019)<br><br>Progress report (TBC Nov 2019)<br><br>Final report. Data lock at 36 months (TBC July 2020), report 3 months later (TBC Apr 2020) |

***Risk minimisation measures***

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Treatment of children with mild to moderate sialorrhoea | **Warning in Section 4.4 of the SmPC**: Due to the low likelihood of benefit and the known adverse effect profile, Sialanar should not be given to children with mild to moderate sialorrhoea. | Drug Utilisation Study |
| Treatment of patients with severe renal impairment (eGFR <30 ml/min/1.73m$^2$), including those with end-stage renal disease requiring dialysis. | **Contraindication in Section 4.3 of the SmPC**: Severe renal impairment (eGFR <30 ml/min/1.73m$^2$), including those with end-stage renal disease requiring dialysis.<br>**Undesirable effects in Section 4.8 of the SmPC:** Urinary retention was seen very commonly in studies with glycopyrronium.<br>Additionally it warns the prescriber to alert the carer to stop treatment in the case of urinary retention. | Not required. |
| Constipation | **Warning in Section 4.4 of the SmPC**: Anticholinergic effects such as urinary retention, constipation and overheating due to inhibition of sweating may be dose dependent and difficult to assess in a disabled child. Monitoring by physicians and caregivers is required with adherence to the management instructions below:<br><u>Management of important anticholinergic side effects</u><br>The prescriber should alert the carer to stop treatment or reduce the dose and seek advice from the prescriber in the event of constipation.<br>**Undesirable effects in Section 4.8 of the SmPC**: Constipation was seen very commonly in studies The prescriber should alert the carer to stop treatment and seek advice from the prescriber in the event of constipation. | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11)<br>Drug Utilisation Study |
| Urinary retention | **Contraindication in Section 4.3 of the SmPC:** Urinary retention<br>**Warnings in Section 4.4 of the SmPC:** Glycopyrronium can cause urinary retention, which may be difficult to diagnose in a disabled child. Urinary retention may present with signs of discomfort in the child. Glycopyrronium should be discontinued if urinary retention is present.<br>**Undesirable effects in Section 4.8 of the SmPC**: Anticholinergic effects such as urinary retention, constipation and overheating due to inhibition of sweating may be dose dependent and difficult to assess in a disabled child. Monitoring by physicians and caregivers is required with adherence to the management instructions below: | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11)<br>Drug Utilisation Study |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Management of important anticholinergic side effects<br>The prescriber should alert the carer to stop treatment or reduce the dose and seek advice from the prescriber in the event of urinary retention. | |
| Pneumonia | **Warnings in Section 4.4 of the SmPC:**<br>Glycopyrronium can cause thickening of secretions, which may increase the risk of respiratory infection and pneumonia. Glycopyrronium should be discontinued if pneumonia is present.<br>**Undesirable effects in Section 4.8 of the SmPC**:<br>Pneumonia is a known adverse effect but the frequency is unknown. The prescriber should alert the carer to stop treatment and seek advice from the prescriber in the event of pneumonia | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11)<br>Drug Utilisation Study |
| Risk of Over heating | **Warning in Section 4.4 of the SmPC:**<br>Anticholinergic effects such as urinary retention, constipation and overheating due to inhibition of sweating may be dose dependent and difficult to assess in a disabled child. Monitoring by physicians and caregivers is required with adherence to the management instructions below:<br>Management of important anticholinergic side effects<br>The prescriber should alert the carer to stop treatment or reduce the dose and seek advice from the prescriber in the event of:<br>• pyrexia<br>• very hot weather | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11) |
| Overdose | **Posology Section 4.2 of the SmPC** Paediatric population – children and adolescents aged 3 and older<br>The dosing schedule for glycopyrronium is based on the weight of the child, starting with approximately 12.8 micrograms/kg per dose (equivalent to 16 micrograms/kg per dose glycopyrronium bromide), three times per day and increasing by the doses shown in Table 1 below, every 7 days. Dose titration should be continued until efficacy is balanced with undesirable effects and amended up or down as appropriate, to a maximum individual dose of 64 micrograms/kg body weight glycopyrronium or 6 ml (1.9 mg glycopyrronium, equivalent to 2.4 mg glycopyrronium bromide) three | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11) |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | times a day, whichever is less. Dose titrations should be conducted in discussion with the carer to assess both efficacy and undesirable effects until an acceptable maintenance dose is achieved.<br>Undesirable effects may be minimised by using the lowest effective dose necessary to control symptoms. It is important that the carer checks the dose volume in the syringe before administration. The maximum volume of the highest dose is 6ml. In the event of a known anticholinergic adverse event occurring when the dose is increased, the dose should be reduced to the previous lower dose and the event monitored. If the event does not resolve treatment should be discontinued. In the event of constipation, urinary retention or pneumonia treatment should be stopped until the event resolves. Younger children may be more susceptible to adverse events and this should be borne in mind when any dose adjustments are carried out.<br>Following the dose titration period, the child's sialorrhoea should be monitored, in conjunction with the carer, to assess changes in efficacy and/or tolerability over time, and the dose adjusted accordingly.<br><br>**Overdose section 4.9 of the SmPC states:**<br>Symptoms Overdose of glycopyrronium can result in anticholinergic syndrome, produced by the inhibition of cholinergic neurotransmission at muscarinic receptor sites. Clinical manifestations are caused by CNS effects, peripheral nervous system effects, or both. Common manifestations include flushing, dry skin and mucous membranes, mydriasis with loss of accommodation, altered mental status and fever. Additional manifestations include sinus tachycardia, decreased bowel sounds, functional ileus, urinary retention, hypertension, tremulousness and myoclonic jerking. Management Patients presenting with anticholinergic toxicity should be transported to the nearest emergency facility with advanced life support capabilities. Pre-hospital gastrointestinal decontamination with activated charcoal is not recommended because of the potential for somnolence and seizures and the resulting risk of pulmonary aspiration. At hospital, activated charcoal can | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | be administered if the patient's airways can be adequately protected. Physostigmine salicylate is recommended when tachydysrhythmia with subsequent hemodynamic compromise, intractable seizure, severe agitation or psychosis is present.<br>Patients and/or parents/caregivers should be counselled to ensure an acurate dose is given each time, in order to prevent the harmful consequences of anticholinergic reactions of glycopyrronium seen with dosing errors or overdose. The maximum volume for the highest dose is 6mls.<br><br>**PIL Section 3 If you give too much Sialanar to your child.** It is important to make sure an acurate dose is given each time, in order to prevent harmful effects of Sialanar seen with dosing errors or overdose.<br>Check that you have drawn up the correct level on the syringe before giving Sialanar.<br>Seek medical advice immediately if the child is given too much Sialanar, even if the child seems well.<br>**If you forget to give Sialanar**<br>Give the next dose when it is due. Do not give a double dose to make up for the forgotten dose. | |
| Unintentional overdose due to 8ml syringe | **Posology Section 4.2 of the SmPC** *Paediatric population – children and adolescents aged 3 and older*<br><br>The dosing schedule for glycopyrronium is based on the weight of the child, starting with approximately 12.8 micrograms/kg per dose (equivalent to 16 micrograms/kg per dose glycopyrronium bromide), three times per day and increasing by the doses shown in Table 1 below, every 7 days. Dose titration should be continued until efficacy is balanced with undesirable effects and amended up or down as appropriate, to a maximum individual dose of 64 micrograms/kg body weight glycopyrronium or 6 ml (1.9 mg glycopyrronium, equivalent to 2.4 mg glycopyrronium bromide) three times a day, whichever is less. Dose titrations should be conducted in discussion with the carer to assess both efficacy and undesirable effects until an acceptable maintenance dose is achieved.<br><br>Undesirable effects may be minimised by using the lowest effective dose necessary to control symptoms. In the event of a known anticholinergic adverse event occurring when the dose is increased, the dose should be reduced to the previous lower dose and the event monitored. If the event does not resolve treatment | Overdose |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | should be discontinued. In the event of constipation, urinary retention or pneumonia treatment should be stopped until the event resolves.<br><br>Younger children may be more susceptible to adverse events and this should be borne in mind when any dose adjustments are carried out.<br><br>Following the dose titration period, the child's sialorrhoea should be monitored, in conjunction with the carer, to assess changes in efficacy and/or tolerability over time, and the dose adjusted accordingly.<br><br>**Overdose section 4.9 of the SmPC states:**<br>Symptoms Overdose of glycopyrronium can result in anticholinergic syndrome, produced by the inhibition of cholinergic neurotransmission at muscarinic receptor sites. Clinical manifestations are caused by CNS effects, peripheral nervous system effects, or both. Common manifestations include flushing, dry skin and mucous membranes, mydriasis with loss of accommodation, altered mental status and fever. Additional manifestations include sinus tachycardia, decreased bowel sounds, functional ileus, urinary retention, hypertension, tremulousness and myoclonic jerking.<br>Management Patients presenting with anticholinergic toxicity should be transported to the nearest emergency facility with advanced life support capabilities. Pre-hospital gastrointestinal decontamination with activated charcoal is not recommended because of the potential for somnolence and seizures and the resulting risk of pulmonary aspiration. At hospital, activated charcoal can be administered if the patient's airways can be adequately protected. Physostigmine salicylate is recommended when tachydysrhythmia with subsequent hemodynamic compromise, intractable seizure, severe agitation or psychosis is present.<br>Patients and/or parents/caregivers should be counselled to ensure an acurate dose is given each time, in order to prevent the harmful consequences of anticholinergic reactions of glycopyrronium seen with dosing errors or overdose. The maximum volume for the highest dose is 6mls.<br><br>**PIL Section 3 If you give too much Sialanar to your child.** It is important to make sure an acurate dose is given each time, in order to prevent harmful effects of Sialanar seen with dosing errors or overdose.<br><br>Check that you have drawn up the correct level on the syringe before giving Sialanar.<br><br>Seek medical advice immediately if the child is given too much Sialanar, even if the child seems well. | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | **If you forget to give Sialanar**<br>Give the next dose when it is due. Do not give a double dose to make up for the forgotten dose. | |
| Interactions with other medicinal products | **Contraindication in Section 4.3 of the SmPC:**<br>Concomitant treatment with (see section 4.5);<br>*potassium chloride solid oral dose; anticholinergics;*<br><br>**Interactions in section 4.5 of the SmPC:** There are limited data available relating to interactions with other medicinal products in the paediatric age group. The following drug interaction information is relevant to glycopyrronium.<br><br><u>Contraindications of concomitant use</u><br>Concomitant use of the following medicinal products is contraindicated (see section 4.3):<br>*Potassium chloride solid oral dose:* glycopyrronium may potentiate the risk of upper gastrointestinal injury associated with oral solid formulations of potassium chloride due to increased gastrointestinal transit time creating a high localized concentration of potassium ions. An association with upper GI bleeding and small bowel ulceration, stenosis, perforation, and obstruction has been observed.<br>*Anticholinergics*: anticholinergics may delay the gastrointestinal absorption of other anticholinergics administered orally and increase the risk of anticholinergic side effects.<br><br><u>Concomitant use to be considered with caution</u><br><br><u>Concomitant use</u> of the following medicinal products should be <u>considered with caution</u><br><br>*Antispasmodics*: glycopyrronium may antagonize the pharmacologic effects of gastrointestinal prokinetic active substances such as domperidone and metoclopramide.<br><br>*Topiramate*: glycopyrronium may potentiate the effects of oligohidrosis and hyperthermia associated with the use of topiramate, particularly in pediatric patients;<br><br>*Sedating antihistamines*: may have additive anticholinergic effects. A reduction in anticholinergic and/or antihistamine dosage may be necessary;<br>*Neuroleptics/antipsychotics*: the effects of active substances such as phenothiazines, clozapine and haloperidol may be potentiated. A reduction in anticholinergic and/or neuroleptic/antipsychotic dose may be necessary;<br>*Skeletal muscle relaxants*: Use of anticholinergics after administration of botulinum toxin may potentiate systemic anticholinergic effects; | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11) |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | *Tricyclic antidepressants and MAOIs:* may have additive anticholinergic effects. A reduction in anticholinergic and/or tricyclic antidepressants and MAOIs dosage may be necessary.<br><br>*Opioids*: active substances such as pethidine and codeine may result in additive central nervous system and gastrointestinal adverse effects, and increase the risk of severe constipation or paralytic ileus and CNS depression. If concomitant use cannot be avoided, patients should be monitored for potentially excessive or prolonged CNS depression and constipation;<br><br>*Corticosteroids*: Steroid-induced glaucoma may develop with topical, inhaled, oral or intravenous, steroid administration. Concomitant use may result in increased intraocular pressure via an open- or a closed-angle mechanism;<br>*Nitrates*: may decrease the dissolution of sublingual nitroglycerin by inducing dry mouth and decreased salivation resulting in a potential reduction in therapeutic effect;<br><br>Other<br>Medicinal products with anticholinergic properties (e.g. antihistamines, antidepressants) may cause a cumulative parasympatholytic effects including dry mouth, urinary retention, constipation and confusion, and an increased risk of anticholinergic intoxication syndrome. | |
| Cardiac disorders | **Warning in Section 4.4 of the SmPC**: Glycopyrronium should be used with caution in patients with acute myocardial infarction, hypertension, coronary artery disease, cardiac arrhythmias and conditions characterised by tachycardia (including thyrotoxicosis, cardiac insufficiency, cardiac surgery) due to the potential increase in heart rate, blood pressure and rhythm disorders produced by its administration. The carer should be advised to measure the pulse rate if the child seems unwell and report very fast or very slow heart rate.<br>**Undesirable effects in Section 4.8 of the SmPC**<br>Cardiac disorders. Glycopyrronium is known to have an effect on heart rate and blood pressure at doses used during anaesthesia although clinical trials in children with chronic drooling have not shown this effect. An effect on the cardiovascular system should be considered when assessing tolerability. | Not required. |
| Dental Caries | **Warning in Section 4.4 of the SmPC**:<br><br>*Dental*<br>Since reduced salivation can increase the risk of oral cavities and periodontal diseases, it is important that patients receive adequate daily dental hygiene and | Not required |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | regular dental health checks. | |
| CNS effects | **Warning in Section 4.4 of the SmPC**:<br>*CNS adverse events*<br>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.<br>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. | CNS effects |
| Safety in long-term use, beyond 24 weeks has not been established | **Method of administration 4.2 of the SmPC:**<br><br>Due to the lack of long term safety data, Sialanar is recommended for short-term intermittent use (see 4.4)<br><br>**Warnings and precautions 4.4 of the SmPC**:<br>*Lack of long-term safety data*<br>Published safety data are not available beyond 24 weeks treatment duration. Given the limited long-term safety data available and the uncertainties around the potential risk for carcinogenicity, total treatment duration should be kept as short as possible. . If continuous treatment is needed (eg 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".<br><br>**Information in SmPC Section 5.1**<br>**Pharmacodynamic Properties:** The safety and efficacy of glycopyrronium bromide 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 percentage of responders at week 24 was assessed relative to all intent-to-treat patients (n = 137), except for seven patients with missing values. Patients who discontinued treatment due to lack of efficacy had their worst observation carried forward, whereas patients who discontinued due to any other reason had their last observation carried forward. The adverse event profile seen with anticholinergics was demonstrated in children with chronic drooling. No new or different adverse events were seen. | Drug Utilisation Study |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Treatment of children below the age of 3 years | **Posology and method of administration in Section 4.2 of the SmPC**: Sialanar is not recommended in children aged <3 years in the symptomatic treatment of sialorrhoea (chronic pathological drooling) (see section 4.4).<br>**Warning in Section 4.4 of the SmPC**: Sialanar is not recommended in children below the age of 3 years since there is very limited data on the efficacy and safety of glycopyrronium in this age group. | A checklist for HCP and Reminder Card for Care Givers (see Annexes 10 and 11)<br>Drug Utilisation Study |
| Treatment of patients with compromised blood brain barrier | **Warning in Section 4.4 of the SmPC**:<br>*CNS adverse events*<br>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.<br>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. | Not required. |

## *5.2. Pharmacovigilance*

***Pharmacovigilance system***

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

## *5.3. Product information*

### 5.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

# 6. Benefit-risk balance

***Benefits***

***Beneficial effects***

The benefit of glycopyrronium in alleviating pathological drooling in children with neurological disorders has been demonstrated in two randomised, placebo-controlled clinical trials: The Zeller, 2012a study and the Mier, 2000 study. Both studies were short-term as the treatment duration was 8 weeks.

The pivotal 8-week study in Zeller at al. 2012a conducted with thirty-eight patients demonstrated superiority of glycopyrrolate over placebo in reduction of drooling in children 3-16 years old:

The initial dose was 0.02 mg/kg, which was increased in 0.02 m g/kg increments every 5 to 7 days up to a maximum dose of 0.1 mg/kg (but not to exceed a maximum dose of 3 mg t.i.d, regardless of weight). The responder rate at Week 8 (≥ 3 point improvement on the mTDS) was significantly higher for glycopyrrolate (14/19; 73.7%) than for placebo (3/17; 17.6%) (p = 0.0011), with improvements starting 2 weeks after treatment initiation (52.6% vs. 0%; p=0.00007). The favourable effects of GP on the mTDS were corroborated by results of investigator and patient/caregiver rated global assessments. Due to differences in relative bioavailability between Sialanar (approximately 25% higher bioavailability) and the product used in this trial the proposed titration scheme for Sialanar was adapted during the procedure to largely mirror exposure levels obtained during titration in this trial.

Also the study by Mier et al. conducted in thirty-nine children aged 4 years and older with neurodevelopmental conditions and severe sialorrhoea demonstrated superiority of glycopyrrolate over placebo. Doses were increased in 0.6 mg increments in both groups but from different starting doses: 0.6 to 2.4 mg in the lower weight group and 1.2 to 3.0 mg in the higher weight group. Drooling score on the mTDS improved in a linear manner with increasing dose level over the 4-week titration period; scores were 6.0 at dose level 1, 4.5 at level 2, 3.6 at level 3, and 2.6 at level 4. After an additional 4 weeks at the highest individual dose the mean drooling score had decreased further to 2.3.

These two randomised, double-blind studies are supported by a long-term safety study by Zeller at al. 2012b. In this 24-week, open-label study glycopyrrolate was administered to 137 paediatric patients between 3-18 years of age. At Week 24, 52.3% (95% CI 43.7–60.9) of subjects were responders (≥ 3 point reduction on the mTDS). The proportion of responders ranged between 40.3% and 56.7% over the 6 assessment points during the 24 week study period.

***Uncertainty in the knowledge about the beneficial effects***

General uncertainties on the beneficial effects within this bibliographic application are deriving from the study design and the analysis/reporting of both the Zeller 2012a study and, in particular, the Mier study but do not lead to particular concerns. The main efficacy studies were performed with similar formulations of GP than Sialanar. The higher bioavailability of Sialanar compared to the product used in the pivotal Zeller studies (Zeller 2012a and Zeller 2012b) was addressed by revising the titration schedule for Sialanar, addressing the concern on the uncertainty on the applicability of the pivotal data to Sialanar.

With regards to representation of the target population in the submitted studies, the Applicant has provided information from the pivotal submitted publications, supporting that children with severe drooling (as defined by the modified Teacher´s Drooling Scale; mTDS scores of 6 and above relate to severe and profuse

drooling.) were included and also constituted the majority of the patients in the studies.In the Zeller, 2012a study, included patients had severe drooling (mTDS score of 6 or higher) and in the study by Mier, 2000, mean baseline drooling scores were 7.52 for glycopyrronium and 7.44 for placebo. In Zeller 2012b, 68.2% of children had baseline drooling which was severe or profuse in nature. This provides sufficient certainty about the applicability of the efficacy data to the narrower indication of severely affected patients which was implemented during this re-examination procedure.

The two placebo-controlled studies only investigated efficacy in the short-term and although the open-label study Zeller 2012b offers some reassurance about maintenance of the effect over 24 weeks maintenance of efficacy for long term or chronic use could not be fully substantiated by the available data. As advised by the ad hoc expert group the sparse long term data and the long-term benefit risk can, however, be weighed against the severity of the child sialorrhoea and the underlying disease and monitoring the effect on siallorhea following dose titration as now outlined in the SmPC takes due account of potential loss of efficacy should treatment be prolonged in the palliative care setting. Outside the palliative care setting Sialanar should only be given for short-term intermittent use as outlined in the SmPC.

***Risks***

***Unfavourable effects***

The plasma concentration of GP required for effective vagolysis has been determined to be at least 10 µg/L. In studies in children by Rautokorpi et al, 1994 and Rautokorpi et al, 1998 plasma concentrations following a 5 µg/kg i.v. dose of GP only briefly exceeded this concentration immediately following administration. In study PRO/GLY/001, the maximum plasma concentration after 2 mg (~0.03 mg/kg) of Sialanar in adult volunteers occurred between 3 and 7 hours post dose, reaching a maxima of ~1000 pg/mL (i.e. 1 µg/L). The highest dose of Sialanar (0.1 mg/kg) in the Applicant's proposed posology is 3.3 fold higher than the average dose (in mg/kg terms) tested in PRO/GLY/001. It is therefore conceivable, given the variability in exposure to GP after oral administration, that some paediatric patients at the highest dose(s) may briefly attain a plasma concentration of GP sufficient to cause a vagolytic effect. The numbers of occurrences of cardiac events in CPRD were extremely low. To take due account of the remaining risk the SmPC informs about cardiac effects and outlines that effects on the cardiovascular system should be considered when assessing tolerability. Additionally robust educational material was established addressing this issue which is considered to be sufficient in this setting considering that the ad hoc expert group considered caretakers in general highly skilled to evaluate the well-being of their patients.

GP passes the BBB in very limited amount except in situations where the BBB has been compromised e.g. by a shunt infection. However in the study of Mier there was a higher frequency of AEs related to CNS (23%) in the GP group compared to placebo. The Applicant points to that the dose in the Mier study was higher but still, this raises concern that some children treated have a more pronounced risk of transfer of GP into CNS. The main concern of the CHMP was that in the case of CNS adverse effects these may be difficult to assess for the caregiver and depending on the neurological disease with fluctuations of alertness can be difficult to distinguish from side effects of the medication.

The ad hoc experts acknowledged that potential effect on CNS may be seen with the use of GP, but based on their experience this was not a common adverse event and may not be a serious problem in severely affected patients who are taking in general multiple medications with CNS effects and have a significant benefit with their drooling control. This was taken into consideration by the CHMP together with the expert's view that caregivers / parents of these patients are highly skillful to detect changes in the behavior of their children.

Considering the narrower indication (severely affected patients) and the particular clinical benefit of these patients available data with respect to potential risk of CNS effect was considered as sufficient and a potential risk was considered acceptable with the warning included into the SmPC on CNS adverse effects and the established risk minimization measures.

Another serious side effect is pneumonia and the data from Zeller 2012(b) suggests a causal relationship with GP. Therefore advice was added to SmPC and educational material that, should pneumonia occur, the treatment should be discontinued. The experts raised that inappropriate dosing of GP leads to thick mucus and pneumonia and that this risk can be considered manageable with careful titration. Obstipation is a further side effect that may be severe in this setting of patients because this may also be a result of the low degree of physical activity in the patients. However, based on the deliberations of the experts this side effect is considered sufficiently detectable by a caregiver trained with adequate educational material if advised to be attentive to this risk.

Based on the expert feedback the CHMP considers both, pneumonia (via over drying) and obstipation to be manageable by the trained and experience caregiver and prescriber as they are detectable and mostly results of inappropriate titration. This key problem is now sufficiently addressed by educational material and the planned DUS (as outlined in the RMP). Taking all this into consideration, the CHMP concluded that the submitted data referring to these adverse events is sufficient for an approval in the new target population.

Urinary retention was reported with an incidence of 13-15% with GP in randomized controlled clinical studies whereas not occurring in the placebo arm and there was neither information provided on the severity of the episodes of urinary retention nor if it was associated with an increased incidence of urinary tract infections. This risk of urinary retention was acknowledged by the experts even though not commonly seen in the treated patients in clinical practice. The experts considered urinary retention sufficiently detectable by the caregivers (e.g. by urine diary) and manageable with careful titration of the drug by the treating physician together with robust guidance on the identification and management of side effects. The CHMP considers that taking into consideration the expert prescription, the caregivers which were seen as in general very skillful by the ad hoc experts in detecting side effects of their children, the recommendations given in the SmPC and in the educational material on careful titration and recommended action if side effects occur as sufficient to balance the risk of urinary retention. An age appropriate formulation of GP such as Sialanar may also facilitate titration as outlined by the expert. Furthermore the implemented DUS addresses further the underlying problem of inadequate titration which was stressed by the ad hoc experts. Together with the implemented short-term intermittent use and recommendations in the SmPC on considering carefully the benefit risk of the patient if treatment is repeated sufficient assurance is given on the control of this risk.

Dry mouth is probably an inevitable side effect of GP as this is the effect that the treatment is aiming for. It is known that dry mouth is a severe risk factor for caries and a high level of mouth hygiene is necessary. As these patients need general anaesthesia in relation to dental visits robust educational material for the caregivers is put in place as emphasized by the experts which is considered to control sufficiently for this risk.

***Uncertainty in the knowledge about the unfavourable effects***

The data submitted support short-term treatment but there are limited long term data (24 weeks and controlled data only 12 weeks). Since the substance is well known it is reasonable to believe that the long term adverse events relating to the anticholinergic effect are similar to those seen in more short term. However, some potential long term safety concerns are less well characterized.

CHMP's concern regarding animal data on repeat use toxicology and extrapolation of safety margins to the

proposed population (chronic treatment of all severity grades of siallorhea) could only be addressed by the treatment duration restriction to short term-intermittent use. That no exposure data are available from repeated dose toxicology studies with glycopyrronium is also outlined in the SmPC to inform the prescriber. The CHMP took also into consideration that the safety profile was considered by the ad hoc experts to be predictable and manageable with the applied dose titration scheme, educational material and monitoring of the benefit/risk balance of the medicinal product.

Submitted publications did not contain animal data regarding genotoxicity or carcinogenicity and only a very brief presentation of reproductive toxicity data from one study in rats showing no abnormalities attributed to drug administration in offspring. This was not considered to be acceptable for the claimed indication of chronic treatment of siallorhea in all grades of severity. The CHMP acknowledges that a carcinogenic potential of GP has not been reported within the therapeutic class and clinical data from the CPRD do not show evidence that glycopyrronium causes reproductive or developmental toxicity and also no evidence of a carcinogenic potential in this patient population. Nevertheless, in the absence of dedicated animal studies with Sialanar, this uncertainty was only considered acceptable with the recommendations of control and reduction of exposure taking into consideration the individual patients profile as outlined in the SmPC. Furthermore the short-term intermittent use and the monitoring of the benefit risk profile by the treating physician make this remaining uncertainty acceptable.

Considering the short term intermittent use concerns on reproductive and developmental toxicity can also be considered sufficiently addressed in this patient population together with the inclusion of a contraindication in pregnancy / breast feeding women, requiring contraception where applicable and outlining the sparse non clinical data in 5.3 of the SmPC.

Deficiencies in robust long-term data and the long term benefit risk were also acknowledged by the experts who emphasized however that needs should be seen in the context of the severity of the disease. Therefore in the palliative care situation due to the particular benefit risk profile of these patients continuous treatment can be considered as also in situation where treatment needs to be repeated intermittently. However benefits and risks should be carefully considered on a case by case basis and treatment should be closely monitored in this setting as outlined in the SmPC.

No data was submitted in patients below the age of 3 and the safety profile for these patients remains to be inappropriately characterized. The use in these patients is not recommended according to the SmPC however according to the experts, there may be particular circumstances such as at the end of live where Glycopyrronium may have a use in therapy for younger patients.

**Table 25 Effects Table**

Effects Table for Sialanar (glycopyrronium bromide) for sialorrhoea (chronic pathological drooling) in children with neurological disorders.

| Effect | Short Description | Unit | Treatment (glycol-pyrronium) | Control (placebo) | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| mTDS responder | Proportion with ≥3-point improvement at week 8 | n/N (%) | 14/19 (73.7) | 3/17 (17.6) | p = 0.0011 | Zeller et al, 2012a |
| mTDS | Mean improvement at week 8 | | 3.94 | 0.71 | P < 0.0001 | Zeller et al, 2012a |

| Effect | Short Description | Unit | Treatment (glycol-pyrronium) | Control (placebo) | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Investigator global assessment | Proportion rated as worthwhile | % | 84.2 | 41.2 | p = 0.0140 | Zeller et al, 2012a |
| Patient/care giver global assessment | Proportion rated as worthwhile | % | 100% | 56.3 | p = 0.0017 | Zeller et al, 2012 |
| Drooling score | Mean score following treatment | | 1.85 | 6.33 | p < 0.001<br>Study setup very different from recommended use of Sialanar | Mier et al, 2000 |
| Drooling score, dose response | Mean score after 4 weeks at highest dose by dose level | | Level 1: 6.0<br>Level 2: 4.5<br>Level 3: 3.6<br>Level 4: 2.3 | | No CI or p-values reported | Mier et al, 2000 |
| Drooling score responder, dose responder | Proportion with ≥4-point improvement by dose level | % | Level 1: 12<br>Level 2: 38<br>Level 3: 54<br>Level 4: 81 | | No CI or p-values reported | Mier et al, 2000 |
| **Unfavourable Effects** | | | | | | |
| Dry mouth and Excessive dryness of mouth or secretions | | % | 18-40 | 0-11 | | Zeller et al, 2012a and Mier et al, 2000 |
| Constipation | | % | 18-30 | 0-22 | | Zeller et al, 2012a and Mier et al, 2000 |
| Vomiting | | % | 10-30 | 0-11 | | Zeller et al, 2012a and Mier et al, 2000 |
| Nasal congestion | | % | 10-30 | 3-5 | | Zeller et al, 2012a and Mier et al, 2000 |
| Flushing | | % | 10-25 | 3-17 | | Zeller et al, 2012a and Mier et al, 2000 |
| Behavioural changes | Includes drowsiness, restlessness, overactivity, short attention span, frustration, irritability, mood changes, temper outbursts, explosive behaviour, excessive sensitivity, seriousness, sadness, frequent crying episodes, fearfulness. | % | 23 | 3 | | Mier et al, 2000 |

| Effect | Short Description | Unit | Treatment (glycol-pyrronium) | Control (placebo) | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Urinary retention | | % | 13-15 | 0 | | Zeller et al, 2012a and Mier et al, 2000 |
| Diarrhoea | | % | 10 | 3 | | Mier et al, 2000 |

***Benefit-risk balance***

***Importance of favourable and unfavourable effects***

The submitted data, together with the knowledge about the mechanism of action of GP, support that GP can reduce drooling in the proposed target population. Even though there is limited published data with respect to improvement of QoL associated with GP treatment, the experts at the SAG meeting confirmed that excessive drooling as seen in severe cases is significantly impacting the patient´s quality of life and treatment is an important element of patient care. Aspiration was considered as one of the most important consequences of drooling. In severely affected patients the control of potential reflux in children heavily choking was considered critical to alleviate distress.

Safety AEs are within those expected based on the anticholinergic mechanism of action and most side effects can be controlled ensuring adequate titration and monitoring of side effects by the experienced and trained carer together with the expert prescriber.

In addition to a restriction in the target population, Sialanar is recommended to be prescribed and managed by specialists in the treatment of paediatric patients with neurological disorders, experienced in the treatment of these complex conditions.

Appropriate information to warn physicians on the most relevant AEs has been included in the SmPC in order to prevent and/or minimise these risks. The potential for clinically relevant cardiovascular effects is considered low and manageable with careful titration of the dose by the expert prescriber monitoring the patient. Also potential side effects such as urinary retention and pneumonia appears to be associated with inadequate titration of GP and the product information and the educational material for the expert prescriber as well as for the caregivers are taking due account of this. Furthermore a drug utilization study was included into the RMP to confirm an appropriate application of the recommended titration schedule.

CNS effects have been reported with GP but according to the ad hoc experts they are weighed in their significance in the targeted patient population against the clearly clinical relevant effect of the control of severe drooling.

***Benefit-risk balance***

The Benefit-risk balance is considered to be positive.

***Discussion on the benefit-risk balance***

Different treatment approaches to pathological drooling exist varying from country to country and depending on the severity of the condition. Speech therapy is usually the first treatment in mild to moderate conditions,

but in more severe cases, medical treatment may be indicated. Anticholinergs (Glycopyrronium or Hyoscine patches) are in use in some countries. Together with Botulinustoxin injections physicians choose from this armamentarium depending on treatment response of the individual patient. According to the experts attending the SAG meeting, an age adapted oral formulation of GP would also allow better dose titration helping to individualize the treatment in particular for severely affected patients who are often treated with numerous drugs. In view of the restrictions in the target population to severe siallorhea, the restriction of use to short term and the limitation of exposure the risk profile of Sialanar is considered to be acceptable in view of the clearly clinical relevant effects of the control of drooling.

Finally it is considered that use of the substance in symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders has been well-established in the European Union for at least 10 years with recognised efficacy and an acceptable level of safety as required for a marketing authorisation application under Article 10a of Directive 2001/83/EC.

# 7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the risk-benefit balance of Sialanar in the Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

### *Conditions or restrictions regarding supply and use*

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

### *Other conditions and requirements of the Marketing Authorisation*

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

### *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## • Additional risk minimisation measures

Prior to launch of Sialanar in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objectives of the programme are:

- to provide information on the administration of Sialanar, specifically on the accurate use of the prescribed dosing, the time of administration before the meals, the avoidance of the administration of Sialanar with high fat meals, use of the oral syringe and the need to complete the administration table at the end of the reminder card for patient's carer to remind the carer of the correct dose to be given to the child.
- to provide information on the management and minimisation of anticholinergic reactions, especially on management of constipation, urinary retention, pneumonia, risk of overheating, CNS effects or overdose; and on allergic reactions. In addition, the materials should highlight the difficulty of the detection of anticholinergic reactions in the treated population and the need to decrease the dose to the previous one in case of suspicion of adverse drug reactions and contact the physician. The materials should also cover the need to avoid exposure to hot weather and overheating; risk of caries associated to reduced salivation and need for regular dental hygiene and dental checks and the requirement to check the pulse at regular intervals.

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

- The physician educational material should contain:
    - The Summary of Product Characteristics
    - Information about the drug utilisation study to monitor and assess effectiveness of additional risk minimisation measures for anticholinergic side effects that may be dose dependent and the importance of contributing to such a study
    - 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:
        - Information on the administration of Sialanar
        - 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:
        - Information on the administration of Sialanar
        - Management and minimisation of anticholinergic reactions

## *Paediatric data*

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0240/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX 1

DIVERGENT POSITION DATED 21 JULY 2016

DIVERGENT POSITION DATED 21 JULY 2016

Sialanar EMEA/H/C/003883

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation for Sialanar indicated for symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

The reasons for divergent opinion were the following:

- The overall safety and tolerability profile of Sialanar in the target population has not appropriately been characterised. There is insufficiently detailed safety data as well as long-term safety data. There are significant safety concerns due to the aimed chronic use of Sialanar in the paediatric population affected by the underlying conditions, in particular on the risks of cardiovascular effect, developmental effects, urinary retention and CNS effects. These uncertainties are a major concern in view of the target population, which cannot be addressed adequately by a reduction of the duration of treatment due to the chronicity of the underlying conditions or by warnings and precaution statements in the Product Information.

- The lack of adequate non-clinical data in support of the claimed indication.

In view of the above considerations the undersigned delegates consider the benefit risk of this product to be negative.

Hanne Lomholt Larsen _____

Ondřej Slanař _____