Redacted under Section 40, Section 41 and Section 43 of the Freedom of Information Act.

MODULE 2.5
CLINICAL OVERVIEW

NAME OF PRODUCT:	**GLYCOPYRROLATE 1 MG & 2 MG TABLETS**
ACTIVE SUBSTANCE:	**GLYCOPYRROLATE**
FORMULATION:	**TABLET (1 MG & 2 MG)**
DATE OF REPORT:	**OCT 2020**

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2.5 CLINICAL OVERVIEW

Background

Sialorrhea (drooling or excessive salivation) is an unintentional loss of saliva from the mouth. Although normal in infants, drooling usually stops when at 15 – 18 months of age and is considered pathologic if present after age 4 years.

The most common cause of sialorrhea is neuromuscular dysfunction; other causes are hypersecretion and sensory or anatomic dysfunction e.g. failure of lip closure or infrequent swallowing. In children with cerebral palsy and other neuromuscular conditions, drooling may be due to hypersalivation and / or oral motor dysfunction.

Drooling can result in perioral chapping, irritation, and maceration, with secondary infection of the facial skin, dehydration due to chronic loss of fluids, and increased risk of silent saliva aspiration that can result in recurrent respiratory infections.

Treatment options explored to control drooling in children and adults include behavioral approaches, such as prompts to swallow or wipe or preventing individuals from putting their fingers or objects into their mouths; surgery to decrease salivary flow and anticholinergic agents such as glycopyrrolate.

[Zeller Robert S. et al 2012(a)].

Introduction

The applicant Kinedexe limited U.K. intends to file an application for marketing authorisation of Glycopyrronium (Glycopyrrolate) Tablets 1 mg and 2 mg for "**use in the treatment of drooling**", in accordance with Article 10(a) of Directive 2001/83/EC, as amended.

Applicant has chosen the well-established route as per Article 10(a) of Directive 2001/83/EC as amended to file its product i.e. Glycopyrrolate Tablet 1 mg and 2 mg. Thus, these applications refer to published scientific literature presented in analogy to the stipulations of Directive 2001/83/EC as amended.

Directive 2001/83/EC (Annex I) lays down specific rules for the demonstration of a well-established medicinal use. The following criteria should be taken into account:

- The time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods;

- The degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments.

- Similarity of the formulations from the literature.

- Recognized efficacy and acceptable level of safety.

Factors which have been taken into account in order to establish a well-established medicinal use of glycopyrronium are:

- Glycopyrrolate (glycopyrronium bromide) is an anticholinergic that has been used in clinical practice to reduce the amount of saliva during generalized anesthesia, and it has been shown to reduce sialorrhea in children with cerebral palsy. (Arbouw M. E. L. et al 2010).

- Glycopyrronium is been used in saliva control and is reported to be preferable to the other anticholinergic drugs because of its long duration of action and inability to cross the blood–brain barrier, thus minimizing central nervous system adverse effects such as sedation, dysphoria, and restlessness. (Reddihough D. S. et al 2011).

- The applicant provided data from the Clinical Practice Research Datalink (CPRD) comprising anonymized electronic health records for 15.5 million patients from 738 primary care practices across the UK. Prescriptions for oral preparations of glycopyrronium (1 mg or 2 mg tablet and liquid) from 2008 were identified. Prescriptions were issued by the primary-care practices contributing to CPRD and 1,083 patients were identified with at least one prescription for oral glycopyrronium from 01 January 2008 to 30 June 2018. This can be considered sufficient to meet the quantitative requirements for well-established use in EU.

- Glycopyrronium is been prescribed in U.K. as a special formulation since years and direct evidence of prescription of last 10 years is available from Prescription Cost Analysis, England 2008 report. (Post Cost Analysis, England, 2008).

The drug is been included in the **BNF data for children published in 2008** which supports the use of glycopyrrolate in the treatment of drooling or hypersalivation.

Page Nos.	Discussion
754	Glycopyrronium is used to control excessive secretions in upper airways or hypersalivation in palliative care.
755	Glycopyrronium is indicated in the control of upper airways secretion and hypersalivation.

	Recommended dosage via oral route is 40 – 100 micrograms / kg, 3 to 4 times per day in children 1 month to 18 years of age. Dose can be adjusted according to response.
756	Glycopyrronium can be administered by mouth, injection solution may be given, or crushed tablets suspended in water. Glycopyrronium Tablets 1 mg and 2 mg are available on a named – patient basis from specialist importing companies.

This supports the use of glycopyrronium bromide oral solution in U.K. over the last 10 years.

- Neurodisability and community paediatricians from across the U.K. were recruited at the 2010 British Academy of Childhood Disability Conference; an anonymous questionnaire was distributed in delegates' conference packs. Paediatricians were told that data would be used to inform the design of a UK study of the effectiveness of interventions for drooling in children with neurodisability. All respondents either prescribed drooling interventions themselves or referred children to other drooling services. Of the 148 paediatricians who prescribed, suggested or referred for medications, 70.3% used glycopyrronium bromide. The second most common prescribing pattern was glycopyrronium bromide as first-line medication (12.9%). (Parr J. R. et al 2012) This also supports the well-established use of glycopyrronium bromide oral solution in U.K.

- The coherence of scientific assessments is discussed in the Clinical Overview (**Module 2.5**).

- Recognized efficacy and acceptable level of safety is discussed in the clinical overview sections (**Module 2.5**).

- For similarity of the formulation from the literature, two efficacy and safety studies from Zeller Robert S. et al 2012(a) and Zeller Robert S. et al 2012(b) discussed in the efficacy and safety section of clinical overview in which glycopyrrolate oral solution (Cuvposa) compared with placebo.

- A bioequivalence study between Kinedexe Glycopyrrolate Tablet and Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate was conducted and is discussed in respective section of clinical overview below. The bioequivalence study (Study No. 934-19) was conducted to bridge with the published Zeller Robert S. et al 2012(a) and Zeller Robert S. et al 2012(b) studies.

Accordingly, it is reasonable and justified that the application is filed in accordance with Article 10(a) of Directive 2001/83/EC as amended. The active substance of the medicinal

products has well established use and is acknowledged as being both, efficient and possessing an acceptable level of safety. This can be derived from the fact that a variety of formulations containing glycopyrrolate have been used in European countries for more than 10 years and have proved to be both safe and effective during their use. Therefore, no additional clinical or pre-clinical studies have been performed by the applicant with the medicinal product under consideration.

The degree of scientific interest allowing detailed assessment of the compound's safety and efficacy is reflected in numerous publications, these articles were evaluated for their relevance and accordingly summarised in Nonclinical and Clinical Overview. Therefore, marketing authorisation in accordance with Article 10(a) of Directive 2001/83/EC as amended can be granted.

The summary of product characteristic (SmPC) included in this application has been drawn by the applicant. Due to their age, it cannot be taken as granted that all published studies cited in the Clinical Overview were conducted in accordance with current Good Clinical Practice (GCP) requirements. Even if some studies were not conducted according to GCP, this is not expected to affect the overall conclusions of this overview. These studies together with the long-term use of glycopyrrolate provide sufficient information on their efficacy in the claimed indication and a sufficiently broad margin of safety. Thus, additional studies conducted according to GCP would not provide further information and are not planned by the applicant. The aim of this Clinical Overview is to provide concise and up-to-date information, referring to products containing glycopyrrolate as their active ingredient. This Clinical Overview particularly focuses on glycopyrrolate, used for the treatment of drooling.

In particular, the overview will address the recently published literature so that any new information on the safety and efficacy of the drug can be taken into account. A critical evaluation of the findings will then be presented in the sections printed in *italics*.

Bibliographic Search Strategy

Since glycopyrrolate has been marketed for many decades worldwide, comprehensive information exists on its biochemistry, pharmacology, safety/toxicology and clinical use. The purpose of this module (Module 2.5: Clinical Overview) is to evaluate the possible efficacy and safety of glycopyrronium through published scientific literature. Furthermore, it will be ascertained whether the SmPC reflects the current state of knowledge on the pharmacology, efficacy and safety of glycopyrrolate. The overview will address the published literature using sources like Medline/PubMed. A PubMed search was performed for Clinical literature of glycopyrrolate in August 2020. The details of the literature search are presented in the below text:

For Module 2.5 (Clinical Overview) literature search was performed for clinical pharmacology, efficacy and safety related to glycopyrronium by using various Boolean search

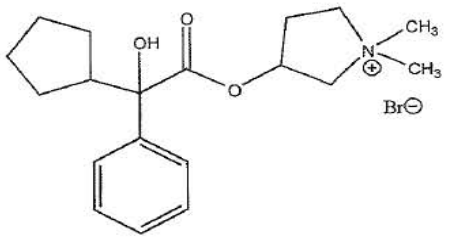
strings like “glycopyrronium”; “glycopyrronium or glycopyrrolate”; “glycopyrronium and drooling” with the limits of “Human” and “English language” with no date limits. These articles were evaluated for their relevance and accordingly summarised in this document. Apart from PubMed/ Medline, various other sources like Guidelines, Books and Compendium were also evaluated for glycopyrronium efficacy and safety and relevant information from these sources are included in this document.

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Glycopyrrolate is an anticholinergic drug.

The chemical name for glycopyrrolate is pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, bromide.

Chemical structure is:



Empirical formula: $C_{19}H_{28}BrNO_3$

Molecular weight: 398.33.

(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

Glycopyrrolate occurs as a white, odorless crystalline powder. It is soluble in water and alcohol and practically insoluble in chloroform and ether. It is completely ionized at physiological pH values. (Glycopyrrolate Oral Solution, FDA Review, 2010).

Glycopyrrolate exists in four distinct stereoisometric forms due to the presence of two chiral centers in the Glycopyrrolate molecule. One of the two enantiomeric pairs of diastereomers of Glycopyrrolate is (R, R)-glycopyrrolate and (S, S)-glycopyrrolate, and the other enantiomeric pair is (R, S)-glycopyrrolate and (S, R)-glycopyrrolate. (Roberts Alan et al 2009).

Indication:

Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Applicant has performed two pilot pharmacokinetic bioavailability studies on Glycopyrrolate1 mg / 5 mL oral solution and Glycopyrrolate 2 mg Tablets with study code. BE/13/061 and 13-021. Both the studies were conducted on healthy adult human male subjects under fasting conditions and performed in accordance with the ICH-GCP practices and applicable regulatory requirements.

BNF data for children published in 2008, supports the use of glycopyrrolate in UK for the treatment of drooling or hypersalivation more than 10 years. Hence to support this indication and as per MHRA recommendation, applicant decided to conduct bioequivalence study with well-established drug (Cuvposa®) for drooling or hypersalivation.

From the data of earlier both the pilot pharmacokinetic study applicant made following conclusions

- Based on the performed pilot pharmacokinetic studies applicant observed high intrasubject variability for Glycopyrronium bromide. The highest reported intra subject variability among both the study was 33.66%.

- Applicant found that considering the observed high intra subject variability for Glycopyrronium bromide, the two-way cross over study design which was used in earlier both the pharmacokinetic studies was not appropriate to prove the bioequivalence between the test and reference product of Glycopyrronium bromide. Full replicate design can be a better option for the bioequivalence assessment of Glycopyrronium bromide.

  Applicant has performed sample size estimation for full replicate design study considering high intra subject variability more than 30% and possible T/R ratio between test and reference product up to ≈ 92% and found that study can meet the bioequivalence criteria with below mentioned sample size.

  T/R ratio ≈ 92 %
  Intra-Subject C.V (%) = ~32.30 %
  Significance Level = 5%
  Power >= 80%
  Bioequivalence Limits = 80.00 – 125.00%

  Based on the above estimate, a sample size of 64 subjects were found required to establish the bioequivalence between the test and reference product. Considering ~10% drop out and discontinued subject, 72 subjects were considered to be sufficient to establish bioequivalence between the test and reference product.

Based on the above sample size justification and justification for the study design applicant has planned and performed a full replicate bioequivalence study comparing Glycopyrronium Bromide 2mg Tablets. The data on open label, single dose, four-period, fully replicate cross over, oral bioequivalence study comparing Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK (test formulation)with Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC(reference formulation).

Study No.: 934-19

Study Design:

A randomized, open-label, single-dose, balanced, crossover two-treatment, two-sequence, four-period, fully replicate cross over, study was conducted in healthy, adult, human subjects under fasting conditions comparing Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK (test formulation)with Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC(reference formulation).

Objective and Purpose of Study:

- Primary objective of the study was to compare the rate and extent of absorption of single dose of Glycopyrronium Bromide 2mg Tablets manufactured for Kinedexe UK Limited, UK with Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC administered under fasting conditions in healthy, adult, human subjects in a randomized cross over study.

- To evaluate the safety and tolerability of a single dose of Glycopyrronium Bromide 2mg Tablets when administered orally in healthy, adult, human subjects under fasting conditions.

Treatment Allocation:

The allocation of treatment sequence for each subject in each study period was carried out as per the randomization schedule. In each study period, a single dose of drug product was administered to the subjects after 10.00 hours overnight fasting along with 240 mL of water in sitting posture.

Washout Period:

A wash out period of 05 days was kept between each consecutive dosing period.

Blood Sampling:

Blood samples were collected at pre-dose (-02.00 to 00.00 hours) was withdrawn before dosing (in the morning on the day of dosing) and the post dose samples at 00.33, 00.67, 01.00, 01.33, 01.67, 02.00, 02.25, 02.50, 02.75, 03.00, 03.25, 03.50, 03.75, 04.00, 04.33, 04.67, 05.00, 06.00, 08.00, 10.00, 12.00, 16.00 and 24.00 hours after dosing in each periodAll blood samples were collected as in-house samples Post-dose samples were collected within +02 minutes from the scheduled time for all samples.

A total of 72 subjects were enrolled as per the protocol. Study was conducted in three groups and subjects were dosed as follows:

Table 01: Dosing details

Period	Group	Total no. of subjects dosed (Subject no. Dosed)
Period I:	Group I	36 (Subject No. [redacted]
	Group II	24 (Subject No. [redacted]
	Group III	12 (Subject No. [redacted]
Period II:	Group I	34 (Subject No. [redacted]
	Group II	21 (Subject No. [redacted]
	Group III	11 (Subject No. [redacted])
Period III	Group I	34 (Subject No. [redacted])
	Group II	17 (Subject No. [redacted])
	Group III	11 (Subject No. [redacted])
Period IV	Group I	34 (Subject No. [redacted])
	Group II	17 (Subject No. [redacted])
	Group III	11 (Subject No. [redacted]
Total 10 (Subject No. [redacted]) subjects dropped out		

Subjects were monitored for adverse events throughout the study. At the end of the study, post study safety evaluation was done which included hematology and clinical bio-chemistry. No severe, serious or life-threatening adverse events occurred during the study. During study from period I check-in (Group-I, II and III) till last PK sample in period IV (Group-I, II and III)) total 22 adverse events were occurred and 10 adverse events were observed during the post study evaluation. Out of 32 AEs, 15 AEs were reported with test product and 17 AEs reported with reference product. All the adverse events were mild in severity. Twenty-two adverse events were judged as definitely related to study drug and 10 adverse events were judged as unlikely related to study drug. In this study performed by the applicant, no serious adverse events were reported and the dose was observed to safe and tolerable in healthy adult subjects.

Table 02: The details of the adverse event reported during study are tabulated below:

Sub No.	Adverse Event	Treatment	Period	Severity	Relationship to Drug	Action Taken	Outcome
[redacted]	Dry Mouth	T	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	I	Mild	Definite	Under	Resolved

						Observation	
[redacted]	Dry Mouth	T	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	I	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	II	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	II	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	II	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	II	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	II	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	III	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	III	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	III	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	III	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	IV	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	IV	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	T	IV	Mild	Definite	Under Observation	Resolved
[redacted]	Dry Mouth	R	IV	Mild	Definite	Under Observation	Resolved
[redacted]	Increased Eosinophils count *i.e.* 11.9 % Baseline screening value- 07 % After Repeat Eosinophils count *i.e.* 08%	T	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved
[redacted]	Increased Eosinophils count *i.e.* 13.1 % Baseline screening value- 07 % After Repeat Eosinophils count *i.e.* 07%	R	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved
[redacted]	Increased Eosinophils count *i.e.* 9.9 % Baseline screening value- 08 % After Repeat Eosinophils count *i.e.* 06%	T	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved
[redacted]	Increased Eosinophils count *i.e.* 13.4 % Baseline screening value- 09 % After Repeat Eosinophils	R	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved

	count *i.e.* 09%						
[redacted]*	Increased Eosinophils count *i.e.* 10.0 % Baseline screening value- 3 %	R	Post Study Safety Assessment	Mild	Unlikely	Investigated	Lost to Follow-up
[redacted]*	Increased Eosinophils count *i.e.* 10.2 % Baseline screening value- 08 %	R	Post Study Safety Assessment	Mild	Unlikely	Investigated	Lost to Follow-up
[redacted]	Increased Eosinophils count *i.e.* 10.8 % Baseline screening value- 5.9 % After Repeat Eosinophils count *i.e.* 06%	T	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved
[redacted]	Increased ALT level *i.e.* 168 U/L Baseline screening value- 23 U/L After Repeat ALT level *i.e.* 72 U/L	R	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved
[redacted]	Increased ALT level *i.e.* 190 U/L Baseline screening value- 80 U/L After Repeat ALT level *i.e.* 57 U/L	T	Post Study Safety Assessment	Mild	Unlikely	Investigated	Resolved
[redacted]*	Increased Eosinophils count *i.e.* 14.1 % Baseline screening value- 09 %	R	Post Study Safety Assessment	Mild	Unlikely	Investigated	Lost to Follow-up

T: Test Product, **R:** Reference Product, **NA**: Not Applicable.

*Subjects no. ([redacted] and [redacted] were called and asked about their well-being to which they informed that they are well and do not have any health-related issue. Subjects were reminded about their pending follow-up for post study safety assessment and requested to visit the facility. However, Subjects told that they will not able to come for follow-up.

All reported adverse events were resolved completely without any sequelae except subject no. [redacted] and [redacted](subject did not report to the facility for post study safety assessment follow-up. Hence, considered to be lost to follow-up).

Pharmacokinetic Results:

Pharmacokinetic analysis was done by Non-compartmental method of analysis using the Phoenix WinNonlin® Software Version 6.3 (Pharsight Corporation, USA) for the following pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}, $AUC\_{\%Extrap}$, T_{max}, $T_{½}$ and K_{el}.

Total 66 subjects completed at least two period (with one test and one reference treatment). Hence 66 subjects were considered for pharmacokinetic analysis.

The mean pharmacokinetic parameters of Glycopyrronium for the Test Product (T) and Reference Product (R) are summarized below:

Table 03: Descriptive Statistics of Formulation Means for Glycopyrronium

(Test N=128 and Reference N = 128).

PK Parameters (Units)	Glycopyrronium (Mean ± SD)	
	Test (T)	Reference (R)
C_{max} (pg./mL)	642.9620 ± 433.33620	581.0435 ± 316.38537
AUC_{0-t} (hr*pg./mL)	3221.2630 ± 1872.20509	3065.6417 ± 1650.85661
AUC_{0-inf} (hr*pg./mL)	3349.5189 ± 1936.31928	3202.5926 ± 1698.57406
$AUC_{\_\%Extrap}$	3.871 ± 1.9097	4.550 ± 2.3007
T_{max} (hr)	3.641 ± 1.1221	3.840 ± 1.0461
$T_{1/2}$ (hr)	6.583 ± 2.1412	6.840 ± 2.2831
K_{el} (1/hr)	0.12004 ± 0.051305	0.11799 ± 0.055562
Glycopyrronium (Median (Min - Max))		
T_{max} (hr)	4.330 (1.00 - 4.67)	4.330 (1.33 - 8.00)
$T_{1/2}$ (hr)	6.642 (2.36 - 15.45)	7.027 (2.18 - 11.83)

Statistical Method:

ANOVA, two one-sided tests for bioequivalence, 90% CI and ratio analysis for log-transformed pharmacokinetic parameters C_{max} and$AUC_{0-t.}$ were performed. The pharmacokinetic parameters of Glycopyrronium are summarized below.

Table 04: Geometric Least Square Means, Ratios, and 90% Confidence Interval for Glycopyrronium

Test (T) vs Reference (R) (N=66)

Parameters	Geometric Least Square Mean		Ratio (T Vs R) (%)	% ISCV	Power (%)	The 90% confidence Intervals (%)
	T	R				
Ln (C_{max}) (pg./mL)	542.982	510.332	106.40	38.52	99.90	98.52 - 114.91
Ln (AUC_{0-t}) (hr*pg./mL)	2645.737	2524.977	104.78	32.77	99.96	97.37 -112.76

Conclusion:

- As reported in the literature and in pharmacokinetic study 013-21, high intra subject variability was observed in the study 934-19 also.

- The 90% confidence intervals for the test/reference ratios of the geometric least squares means between test and reference formulations calculated for primary pharmacokinetic parameter C_{max} and AUC_{0-t} were within the bioequivalence range of 78.86% – 126.79 and 80.00% – 125.00% respectively, for Glycopyrroniumin healthy subjects following single dose of 2 mg under fasting conditions.

- Sample size of 72 subject (including drop out/ discontinued subject) was found sufficient in the study.

- As per the information provided in the clinical study report of the study total 66 subjects were completed at least 01 test and 01 reference treatment in the study. Study was found meeting with the bioequivalence criteria with the 66 subjects.

- The power achieved in the study was 99.90 % for Cmax and 99.96% for AUC confirms that sample was adequate.

- Both the study products were reported to be safe and well tolerated in healthy subjects following single dose administrations.

- The applicant tablet is an uncoated tablet and is known to disintegrate quickly and will get solubilized before it reaches the site of absorption. Apart from the pharmacokinetic data and safety information retrieved from bioequivalence study for the purpose of bridging to the data in the literature, the clinical pharmacology data derived from the literature.

- Bioavailability of the applicant's test product Glycopyrronium bromide 2 mg tablets of Kinedexe Uk. Ltd, UK is found comparable with Cuvposa Solution. Thus, the Applicant's test formulation can be interchangeable with the reference Cuvposa Solution.

Biowaiver Justification for Glycopyrronium Bromide 1mg Tablets:

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for C_{max} and AUC_{0-t} fall within the acceptance criteria range of 78.86- 126.79% % in line with current CHMP guidelines.

The selection of the dose, 2 mg used in the bioequivalence study is justified and according to guidelines. According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr), Glycopyrronium Bromide 1mg Tablets satisfy the conditions for waiver of bioequivalence studies conducted on Glycopyrronium Bromide 2 mg Tablets as discussed below:

[redacted]

- The *in vitro* dissolution characteristic demonstrates that dissolution profiles of Glycopyrronium Bromide 1 mg and 2 mg tablets are similar across the physiological pH range and confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

[redacted]

[redacted]

Since all the requirements to waive bioequivalence studies as mentioned in CHMP Guideline on the Investigation of Bioequivalence – CPMP/EWP/QWP/1401/98- Rev 01 Corr are fulfilled, the bioequivalence study performed on Glycopyrronium Bromide 2 mg tablets can therefore be extended to Glycopyrronium Bromide 1 mg tablets.

Glycopyrrolate Bromide Pharmacokinetic Linearity:

No direct dose proportionality data is available on public domain which proves the pharmacokinetic linearity of Glycopyrrolate tablets from 1 mg to 2 mg. In the past also none of the pharmaceuticals companies like Cuvposa, Sialanar, Robinul, Robinul forte have published pharmacokinetic dose proportionality studies, so, in order to prove the pharmacokinetic linearity between the 1mg and 2 mg strengths applicant has performed the dose proportionality study on 1 mg and 2 mg strengths. The study was performed in accordance with the best ICH-GCP practices. The design and conduct of the study is discussed below

Study No. 068-20:

Study design:

An open-label, balanced, randomized, single-dose, two-sequence, four-period, fully-replicate, crossover study to evaluate the Dose-Proportionality of Glycopyrronium Bromide 1mg and 2mg Tablets manufactured for Kinedexe UK Limited, UK in healthy, adult, human subjects under fasting conditions.

Based on the pharmacokinetic profile of the Glycopyrrolate the study was conducted using full replicate design as the Glycopyrrolate exhibit the high intra subject variability. The study was conducted at [redacted]

Objective and Purpose of Study:

To evaluate the dose-proportionality of Glycopyrronium Bromide Tablets at doses of 1mg and 2mg in healthy, adult, human subjects under fasting conditions.

Number of subjects:

Total 16 healthy male human Subjects were recruited in the study and all 16 subjects were completed the study hence included in the dose proportionality analysis.

Treatment Allocation:

The allocation of treatment sequence for each subject in each study period was carried out as per the randomization schedule. In each study period, a single dose of test product 01 i.e. Glycopyrronium Bromide 1mg Tablets or test product 02 i.e. Glycopyrronium Bromide 2mg Tablets drug product was administered to the subjects after 10.00 hours overnight fasting along with 240 mL of water in sitting posture.

Investigational product details

Table 05: Investigational Product Details

	Test Product 1 (T1)	**Test Product 2 (T2)**
Name	Glycopyrronium Bromide 1mg Tablets	Glycopyrronium Bromide 2mg Tablets
Manufactured for	Kinedexe UK Limited, UK.	Kinedexe UK Limited, UK.
Batch No.	[redacted]	[redacted]
Manufacturing date	[redacted]	[redacted]
Expiry Date	[redacted]	[redacted]
Dose	1 x 1mg	1 x 2mg

Washout Period:

A wash out period of 05 days was kept between each consecutive dosing period.

Blood Sampling:

The pre-dose (0.00 hours) blood sample of 04 mL was be taken not more than one hour prior to dosing in each period. Further samples of 04 mL each were collected at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.33, 4.67, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post-dose.

Safety:

Subjects were monitored for adverse events throughout the study. At the end of the study, post study safety evaluation was done which included hematology and clinical biochemistry. No severe, serious or life-threatening adverse events occurred during the study.

Statistical Analysis criteria:

Pharmacokinetic of the Glycopyrronium Bromide 1mg and 2mg tablets will be considered linear if the difference in dose adjusted mean AUCs is no more than 25% when comparing the 1mg and 2 mg strength.

Dose proportionality will be concluded based on slope calculated using the power model criteria. In case of insufficient data for modelling, graphical presentation can be used to evaluate dose proportionality

Statistical Results:

Following are the statistical analysis results of the dose proportionality study 068-20.

Table 06: Geometric Least Squares Mean, Ratio and Difference in Dose Adjusted Mean AUC (%) (N = 16)

PK Parameters (Unit)	Ln- transformed Geometric Least Squares Mean		Ratio (%)	Difference in dose adjusted mean AUC (%)
	Test Product 1 (T1)	Test Product 2 (T2)		
$AUC_{0-t\ normalized}$ (pg.hr/mL)	1660.612	1889.872	87.87	12.13
$AUC_{0-\infty\ normalized}$ (pg.hr/mL)	1745.375	1970.148	88.59	11.41

Table 07: Slope and Modified acceptance range of AUC_{0-t} and $AUC_{0-\infty}$ (N=16)

PK Parameters	Slope	Modified acceptance range
AUC_{0-t}	1.18657	0.6781 – 1.3219
$AUC_{0-\infty}$	1.17477	0.6781 – 1.3219

Conclusion:

As per GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, pharmacokinetics is

considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength. In the dose proportionality study of the Glycopyrronium Bromide , the ratio of test product 1 (T1) and test product 2 (T2) for the Ln-transformed dose-normalized pharmacokinetic parameters AUC0-t and AUC0-∞ for Glycopyrronium was found to be 87.87%, 88.59% respectively. This indicates that difference in dose adjusted mean AUC is 12.13% and 11.41% for AUC0-t and AUC0-∞ respectively.

The slope calculated using the power model criteria for AUC0-t and AUC0-∞ were 1.18657 and 1.17477 and were within modified acceptance range of 0.6780 – 1.3219, respectively.

The study results indicate that two strength formulations of Glycopyrronium Bromide tablets (1 mg and 2 mg) exhibited linear pharmacokinetics and that 1 mg and 2 mg of Glycopyrronium Bromide tablets were dose proportional in healthy subjects.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Mode of Action

Glycopyrrolate, like other anticholinergic (antimuscarinic) agents, inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions. Glycopyrrolate antagonizes muscarinic symptoms (e.g., bronchorrhea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases. The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to atropine sulfate and scopolamine hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily. [Robinul Forte (Glycopyrrolate) Tablets, FDA Label, Shionogi Inc., USA, 2011]

Glycopyrrolate is a competitive inhibitor of acetylcholine (muscarinic) receptors located on peripheral tissues, salivary glands (Cuvposa Oral Solution, Connecticare, 2013), smooth muscle, cardiac muscle, sinoatrial and atrioventricular nodes, exocrine glands and to a lesser degree, autonomic ganglia. Inhibition of these receptors on salivary glands stops the parasympathetic nerve impulses, indirectly reducing the rate of salivation. Glycopyrrolate has little effect on cholinergic stimuli at nicotinic acetylcholine receptors, on structures innervated by postganglionic cholinergic neurons, and on smooth muscles that respond to acetylcholine but have no cholinergic innervation. Unlike other anticholinergics such as atropine and scopolamine, glycopyrrolate has only limited ability to cross lipid membranes such as the blood-brain barrier. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018; Buck Marcia L. et al 2010; Wadhawan R. et al 2014 and Garnock-Jones Karly P. et al 2012).

Glycopyrrolate has a rapid onset of effect, within 1 – 5 minutes when injected intravenously and within 15 – 30 minutes when given orally. Peak effect occurs within 1 – 4 hours with duration of action up to 8 – 12 hours (Garnock-Jones Karly P. et al 2012), depending on individual response. It is reported to be particularly useful if a child is troubled by secretions at night time. (Reddihough D. S. et al 2011).

2.5.3.2 Pharmacodynamics

Anti sialogogue effect

Glycopyrrolate is an anticholinergic quaternary ammonium compound available in oral or parenteral forms and has been used as a pre-anaesthetic agent. It has been found to be 5 – 6 times more potent than atropine in its antisialogogue effect and to have a selective and prolonged effect on salivary secretion and less consistently on sweat glands. It has minimal cardiovascular, ocular and central nervous system effects. When given orally, some reduction in secretion occurs at 2 hours with significant reduction at 6hours, because of its slow absorption from the gastrointestinal tract. Dryness of the mouth is said to persist for nearly 24 hours. (Stern L. M. et al 1997).

Several studies have investigated the effects of glycopyrrolate in various formulations (intravenous, intramuscular and oral) on various bodily functions, including salivation. Glycopyrrolate in all three formulations reduced salivation in healthy adult volunteers, with oral administration showing a delayed onset and longer duration of reduced salivation compared with the two injected formulations. Sweat gland activity was affected in a similar fashion but less consistently and other parameters were mostly unaffected. (Mirakhur R. K. et al 1978 and Mirakhur R. K. et al 1977). Moreover, intra muscular glycopyrrolate appeared to be 5- to 6- fold more potent than intramuscular atropine at reducing salivation. (Garnock-Jones Karly P. et al 2012).

The effects of glycopyrrolate varied in a dose-related manner from slight with lower doses to a marked and persistent effect with higher doses. The intramuscular injection of 0.1 mg caused a maximum reduction in salivary secretion to about 38% (7.0 ml to 4.4 ml) at 2 h, this being a significant. Apart from this 0.1 mg intramuscularly produced insignificant reduction in salivation throughout the period of study. The higher doses tended to produce an early and profound effect on salivary secretion. This was reduced to about 35% (6.5 ml to 2.2 ml) and 25% (6.5 ml to 1.6 ml) at 1 or 2 h respectively after 0.2 mg intramuscularly and was significantly depressed up to 4 h after administration. With 0.4 mg intramuscularly, the depression in salivation was significant throughout the period of study and secretion was less than 15% of its original volume (6.7 ml to 0.8 ml) between 1 and 3 h. When given orally 2.0 mg had little effect, 4.0 mg caused significant salivary significant depression from 4 to 6 h (maximum to 50% of control value at 6 h), while with 8.0 mg, significant reduction occurred after 3 h. (Mirakhur R. K. et al 1978)

In vitro, glycopyrrolate had high affinity and potency towards the M_3 muscarinic receptor (involved with salivation) with an equilibrium dissociation constant (pA_2) of 9.7. The dissociation half-life from the M_3 receptor was 6.1 hours. Glycopyrrolate binding affinities against all five human muscarinic receptor subtypes were similar to each other; the -log inhibitory constant (pKi) for the human M_1, M_2, M_3, M_4 and M_5 receptors were, respectively, 10.09, 9.67, 10.04, 10.26, and 9.74. Corresponding values for atropine, another antimuscarinic agent, were 9.77, 9.47, 9.68, 9.97, and 9.50. (Garnock-Jones Karly P. et al 2012).

Effect of glycopyrrolate for Clozapine induced Sialorrhea is associated with its nonselective antimuscarinic activity combined with potent antagonistic effects at the M3-muscarinic receptor, with the most important role being in salivation. (Liang Chih-Sung et al 2010).

Effect of glycopyrrolate was evaluated on the oral mucous host defence capacity in 12 healthy subjects following a single intravenous dose of glycopyrrolate (4 mg/kg) or placebo (saline) in a randomized, double-blinded, cross-over study. Salivary flow rates were decreased significantly for 12 h after glycopyrrolate injection, compared with saline injection. The concentrations of immunologic and non-immunologic defence factors were increased in the glycopyrrolate group, and differences between the groups were found for all factors except lysozyme and total salivary peroxidase. Compared with baseline values, the secretion rates of all host defence factors generally decreased after the injection of glycopyrrolate but increased after the injection of saline. Glycopyrrolate thus decreases the output of salivary host defence factors into the oral cavity. (Lahteenmaki Merja T. et al 2000)

A comprehensive evaluation of the antimuscarinic effects of glycopyrrolate was done in healthy volunteers. In this study, volunteers received three doses of glycopyrrolate (0.1, 0.2 and 0.4 mg) intramuscularly. three doses (0.1, 0.14 and 0.2 mg) intravenously and three doses (2.0, 4.0. and 8.0 mg) orally. Their effects on salivation, sweat gland activity, heart rate, pupil size and visual accommodation were recorded. The most prominent feature observed was a dose related inhibition of salivary secretion which persisted for over 6 hours after the largest parenteral doses. Sweat gland activity was similarly reduced following glycopyrrolate administration. The studies in healthy volunteers thus clearly show considerable differences in the pharmacological actions of glycopyrrolate and atropine. The most important of these are summarised in table below: (Mirakhur R. K. et al 1983)

Table 08: Summary of principal effects of atropine and glycopyrrolate in volunteers

	Atropine	Glycopyrrolate
Salivation	Marked inhibition	Marked and prolonged inhibition
Sweat glands	Marked inhibition	Marked and prolonged inhibition
Heart rate	Increase	Minimal change
Pupil size	Increase	No change
Near point of vision	Increase	No change

Central Nervous System

As glycopyrrolate possesses a highly polar quaternary ammonium group, its passage across lipid membranes (e.g. the blood-brain barrier) is limited, unlike some other antimuscarinic agents (e.g. atropine). A study involving patients aged 1 month to 9 years with hydrocephalus reported that intravenous atropine 10 mg/kg (n = 7) appeared to have greater penetration of the blood-brain barrier than intravenous glycopyrrolate 5 mg/kg (n = 9), but that cerebrospinal fluid (CSF) infection may be associated with glycopyrrolate penetration. Atropine was found in the CSF of all its recipients, glycopyrrolate in only four of nine (two of whom had clear CSF infections). The CSF/serum concentration ratios were 0.45 and 0.14, respectively; muscarinic receptor occupancies were 45% and 25%. (Garnock-Jones Karly P. et al 2012).

Cardiovascular System

In a pooled population of children with problem drooling associated with neurologic conditions, glycopyrrolate oral solution was associated with a moderate increase from baseline in mean systolic blood pressure (+ 3.4 mm of Hg), a small decrease in mean diastolic blood pressure (-0.3 mm of Hg) and a small (but clinically relevant) increase in mean heart rate (+1.9 beats/min; +10.5 beats/min) in the placebo-controlled study. No changes in mean respiratory rate or body temperature were observed, and the small increase in mean body weight (+ 1.15 kg) may be attributed to normal growth over a 6-month study period. Glycopyrrolate is not expected to have a clinically relevant effect on corrected QT interval duration. (Garnock-Jones Karly P. et al 2012).

Glycopyrrolate is slower in onset and produces less tachycardia than atropine or hyoscine. (Wadhawan R. et al 2014).

Heart rate responses following intravenous glycopyrrolate injection was evaluated in children undergoing surgery. The dose used (5 µg/kg) did not produce any significant heart rate alterations in the pre-induction, post-induction and intraoperative periods in the age-groups studied. This finding can be explained by the quaternary structure of glycopyrrolate, with its slow membrane penetrability and respective slow onset of action on heart rate which may take a few minutes to appear. (Rautakorpi Pirkka et al 1994)

In healthy volunteers the effects on heart rate are insignificant following intravenous administration. Following intravenous administration of the glycopyrrolate in doses ranging from 0.1 to 0.4 mg, no significant changes in heart rate were observed in volunteers. However, the pulse rates of patients rose significantly when the drug was administered as a premedicants. In anaesthetised patients, glycopyrrolate was found to be approximately twice as potent as atropine regarding its ability to increase the heart rate although the peak effect of glycopyrrolate occurred later than that of atropine. When administered to children, glycopyrrolate produced tachycardia. (Mirakhur R. K. et al 1981)

Cardiovascular effects of glycopyrrolate (0.4 mg, n=24) and atropine (0.6 mg, n=24) or scopolamine (0.6 mg, n=22) premedication was studied in healthy women undergoing elective cesarean section or post-partum bilateral tubal ligation following intravenous administration. Maximum increases in heart rate initiated by the premedication's occurred 4 to 6 minutes after injection and were statistically significant with all three drugs. Increases were greater following atropine (35% and 41%, respectively) than after glycopyrrolate (27% and 37%, respectively) or scopolamine (29% and 38%, respectively). Similarly, mean arterial pressure increased more markedly with atropine than with the other two anticholinergics in both groups. of patients but, again, the differences among the three drugs were not statistically significant. In equal antisialogogue doses, circulatory effects of glycopyrrolate are similar to those of scopolamine. Glycopyrrolate offers an advantage only in patients in whom circulatory responses must be depressed and the potential excitement of scopolamine avoided. (Diaz Dolores M. et al 1980)

Abboud Therese et al compared the effects of intravenous atropine and glycopyrrolate on maternal and fatal heart rates and variability, maternal blood pressure, and uterine activity in 20 normal full-term parturient in labour. Group 1 (N=10) received 0.005 mg/kg of glycopyrrolate, and group 2 (N=10) received 0.01 mg/kg of atropine. There were no statistically significant changes in fatal heart rates or variability in either group. Uterine activity increased in a normal manner as labour progressed. Maternal heart rate increased significantly and essentially equally in all patients in both groups. There were no statistically significant changes in maternal blood pressure in either group. (Abboud Therese et al 1983)

Analysis of heart rate variability combined with physiological tests (deep breathing and tilt tests) was used to characterise the effects of atropine and glycopyrrolate on the parasympathetic nervous tone of the heart in healthy male volunteers. The low dose of atropine (120 µg) administered as a continuous infusion in 15 min was associated with parasympatomimetic effects estimated by the slowing of the heart rate and an increase of the mean and beat-to-beat heart rate variability. The bradycardia and increase of heart rate variability following infusion of glycopyrrolate (50 µg) was less marked and did not differ significantly from that of placebo. The higher doses of atropine (720 µg) and glycopyrrolate (300 µg) administered as a continuous infusion in 15 min produced an equal vagal cardiac blockade characterised by significant tachycardia and a decrease in overall and beat-to-beat heart rate variability. It is concluded that at low doses the parasympatomimetic action of glycopyrrolate is less marked than that of atropine; and at higher doses only small differences exist between these two muscarinic antagonists in their effects on cardiac vagal outflow, assessed by heart rate and heart rate variability. (Ali-Melkkila T. et al 1991).

Drollmann et al evaluated the effect of a single inhaled supra-therapeutic dose (8-fold clinical dose in COPD patients) of 400 µg glycopyrronium on the QT interval and other cardiac parameters in healthy subjects. This was a randomized, partially blinded, single-dose, placebo- and positive- (moxifloxacin) controlled, three-way cross-over study. Glycopyrronium did not cause significant QT prolongation compared to placebo however a

slight bradycardic effect at 5 hours post-inhalation was reported. No clinically relevant effects were seen on electrocardiogram (ECG) intervals, or blood pressure. Study results conclude that supra-therapeutic dose of glycopyrronium had a favorable cardiovascular safety profile with no clinically relevant effect on QT interval. (Drollmann Anton et al 2014).

Respiratory System

A study by Gotta and his colleagues showed that glycopyrrolate increased dead space in a similar manner to atropine but for a more prolonged period consistent with the lung duration of action of this drug. This effect is due to anticholinergic-induced bronchodilation. (Gotta Alexander W et al 1981)

Gastrointestinal System

The effects of glycopyrrolate on both the motility and secretions of the gastrointestinal tract (GIT) have been extensively studied. Sun et al and Moeller et al in studies of the effects of the orally administered drug on the GIT noticed a significant decrease in the average volume and acidity of gastric secretions. Although some subsequent studies also demonstrated this effect, it is unlikely to be due to systemically absorbed drug. Glycopyrrolate is thought to be 7-8 times as potent as atropine in its effect on gastric secretions and acidity. In common with other drugs with similar effects, glycopyrrolate also lowers the opening pressure of the lower oesophageal sphincter. The implications of this action may be important for anaesthetists. In addition, it is likely that gastric emptying would be delayed. (Mirakhur R. K. et al 1981)

A study was conducted to determine the effect of glycopyrrolate, on basal gastric secretion and sweat- and salivary-gland activity in 5 volunteers. Volunteers received glycopyrrolate of 0.02 to 0.20 mg s.c. Glycopyrrolate in the injectable form had a significantly greater suppressive effect on basal gastric secretion than on sweating or salivary flow. (Juniper K. et al 1967).

Ocular Effects

Studies in volunteers showed no significant increase in pupillary size or intraocular pressure nor any recession of the near point of vision. (Mirakhur R. K. et al 1981)

2.5.3.3 Pharmacokinetics

Single dose pharmacokinetics of Glycopyrrolate (2 mg) were determined in an open-label, randomized, single-dose, three-treatment, three-period crossover study comparing the bioavailability of the test formulation (Glycopyrrolate oral solution 10 mL; 1 mg / 5 mL) to the marketed tablet product under fasting and fed conditions in healthy subjects. The three treatments were administered alternatively according to the randomization following a 10 hr. fast in fasting condition and immediately after consuming the standard high fat breakfast in

the fed condition. Pre-dose blood samples followed by serial post-dose blood samples were collected in the study in each period. The mean pharmacokinetic parameters are presented below:

Table 09: Pharmacokinetic Parameters for Glycopyrrolate Oral Solution and Tablets

	C_{max} ng / mL	T_{max} hours	AUC_{0-24} ng.h / mL	$AUC_{0-\infty}$ ng.h / mL	$T_{1/2}$ hours
Glycopyrrolate Oral Solution 10 mL; 1 mg / 5 mL (fasting) (N = 37)	0.318 ± 0.190	3.10 ± 1.08	1.74 ±1.07	1.81 ±1.09	3.0 ± 1.2
Glycopyrrolate Oral Solution 10 mL; 1 mg / 5 mL (fed) (N = 36)	0.084 ± 0.081	2.60 ± 1.12	0.38 ± 0.14	0.46 ± 0.13	3.2 ± 1.1
(Glycopyrrolate Tablets 2 mg) (Fasting) (N = 37)	0.406 ± 0.197	3.15 ± 0.863	2.34 ±1.03	2.46 ± 1.15	3.3 ± 1.6

Fasting adults receiving a single dose of glycopyrrolate oral solution 2 mg reached a mean maximum plasma concentration (Cmax) of 0.318 ng/mL after a median time (Tmax) of 2.53 hours (mean Tmax of 3.10 hours).The mean area under the plasma concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$)was 1.81 ng.h / mL

A high-fat meal significantly decreased the absorption of a single dose of glycopyrrolate oral solution 2 mg in healthy adults. When administered under fed conditions, the mean C_{max} and $AUC_{0-\infty}$were both decreased by ≈75% compared with fasting conditions; median and mean T_{max} were not significantly altered. Glycopyrrolate should therefore be administered ⩾1 hour before or ⩾2 hours after meals Results tabulated below:

Table 10: Statistical Analysis for Glycopyrrolate Oral Solution

PK Parameters	Ratio %	90 % Confidence Interval
Liquid Fed vs Liquid Fasted		
C_{max}	26.26	22.34 – 30.86
AUC_{0-24}	24.54	21.15 – 28.48
$AUC_{0-\infty}$	28.91	25.08 – 33.33

(Glycopyrrolate Oral Solution, FDA Review, 2010 and Garnock-Jones Karly P. et al 2012).

Pharmacokinetics of Glycopyrrolate oral Solution 2 mg (1 mg / 5 mL) was studied in healthy subjects to compare the bioavailability of the drug with and without food. Study was designed as a single center, single dose, open-label, two-period crossover trial in healthy subjects. Each

administration was a single oral dose of 2 mg of Glycopyrrolate liquid (1 mg / 5 mL) either without food (Group A) or with food (Group B).

In group A; 10 mL of liquid containing 2 mg of Glycopyrrolate (1 mg / 5 mL) was administered using an oral syringe with 180 mL of water. Subjects were fasted overnight for 10 hours before dosing and 04 hours after the dosing. Water was inhibited for 02 hours after dosing. In group B; 10 mL of liquid containing 2 mg of Glycopyrrolate (1 mg / 5 mL) was administered using an oral syringe with 180 mL of water. Subjects were fasted overnight for 10 hours before high fat, high calorie breakfast and 04 hours after the dosing. Water was inhibited for 02 hours after dosing. A high fat, high calorie breakfast was given to the subjects in 30 minutes prior to dosing and dose of Glycopyrrolate was administered to the subjects immediately (i.e., within 5 minutes) after completion of breakfast. In both the groups, blood samples were collected at pre dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16- and 24-hours post dose.

Table 11: Glycopyrrolate Pharmacokinetic Parameters – Without Food (Group A) vs. With Food (Group B)

Pharmacokinetic Parameters	Fasting Group (A)	Fed Group (B)	Ratio
AUC_{0-24} ng*hr / mL	1.84116	0.48561	3.791
$AUC_{0-\infty}$ng*hr / mL	1.93908	0.60265	3.218
C_{max} ng / mL	0.33727	0.10171	3.316
T_{max} hour	3.15163	2.64802	1.190
K_{el} 1/hour	0.26358	0.22831	1.154
$T_{1/2}$ hour	2.98144	3.25297	0.917

The arithmetic mean AUC_{0-24}hrs for Glycopyrrolate administered under fasted conditions was 1.7361 ± 1.069 ng*hr / mL and for Glycopyrrolate administered under fed conditions was 0.3834 ± 0.1368 ng*hr / mL. Thus, the mean AUC_{0-24}hrs was more than 4.5 times higher in fasting group as compared to fed group. The results for $AUC_{0-\infty}$ were similar as of AUC_{0-24}. Arithmetic mean $AUC_{0-\infty}$ for Glycopyrrolate administered under fasted conditions was 1.8098 ± 1.0878 ng*hr / mL while under fed conditions, the mean was 0.3834 ± 0.1368 ng*hr/mL. The mean $AUC_{0-\infty}$ for fasting group was more than 4.7 times higher than fed group. Arithmetic mean C_{max} of Glycopyrrolate was 0.3178 ± 0.1895 ng / mL and 0.0838 ± 0.0813 ng / mL for fasting and fed group respectively. The mean C_{max} for was about 3.8 times greater in fasting group than the fed group.

The ratio (A/B) of least-square means for AUC_{0-24}, $AUC_{0-\infty}$ and C_{max} were 379.1 %, 321.8% and 331.6% respectively, demonstrating that Glycopyrrolate administered without food increased the extent of absorption. Results conclude that bioavailability of a Glycopyrrolate liquid solution increased when administered without food as compared to the administration of Glycopyrrolate with food.

(Roberts Alan et al 2009).

Pharmacokinetics of glycopyrrolate was evaluated in 12 healthy subjects following single dose intravenous administration of glycopyrrolate (4 mg/kg) and saline (placebo) in a double-blinded, cross-over design, with balanced randomization. The peak plasma glycopyrrolate concentrations (4.92 – 19.35 ng/mL) were reached 2 min after injection in 11 subjects and after 4 min in one subject. The concentrations were less than the detection limit of 0.25 ng/ mL in seven subjects after 2 h, and only two subjects had measurable drug concentrations 3 h after glycopyrrolate injections. The mean half-life of glycopyrrolate in the elimination phase was 34.9 ± 4.4 min. AUC was 151.6 ± 17.6 ng. min/ mL, the clearance was 1.8 ± 0.2 L.h/kg and the distribution volume were 1.4 ± 0.1 L/ kg. (Lahteenmaki Merja T. et al 2000)

Pharmacokinetic properties of glycopyrrolate were evaluated by Ali-Melkkila et al following intravenous, intramuscular and oral administration. After a single intravenous injection, 6 µg/kg (n = 6), glycopyrrolate disappeared very fast from the circulation with a mean distribution phase half-life of 2.22 ± 1.26 min and the elimination phase half-life (0.83 ±0.29 h) and both were short due to the low distribution volume during the elimination phase (0.64 ± 0.29 l/kg) and to the respectively high total plasma clearance value (0.54 ± 0.14 l/kg/h). An intramuscular injection, 8 µg/kg (n = 6), was followed by a fast and predictable systemic drug absorption. The time to maximum plasma concentration (Tmax) was 27.48 ± 6.12 min and the maximum plasma concentration (Cmax) was 3.47 ± 1.48 µg/l. After oral drug intake, 4 mg (n = 6), an apparently low and variable gastrointestinal absorption was found (Tmax = 300.0 ± 197.2 min, Cmax = 0.76 ± 0.35 µg/1), thus indicating that the oral route of drug administration is of no value as a routine premedication. The concentrations of glycopyrrolate in plasma in the three groups of patients can be seen in figures below. (Ali-Melkkila et al 1989)

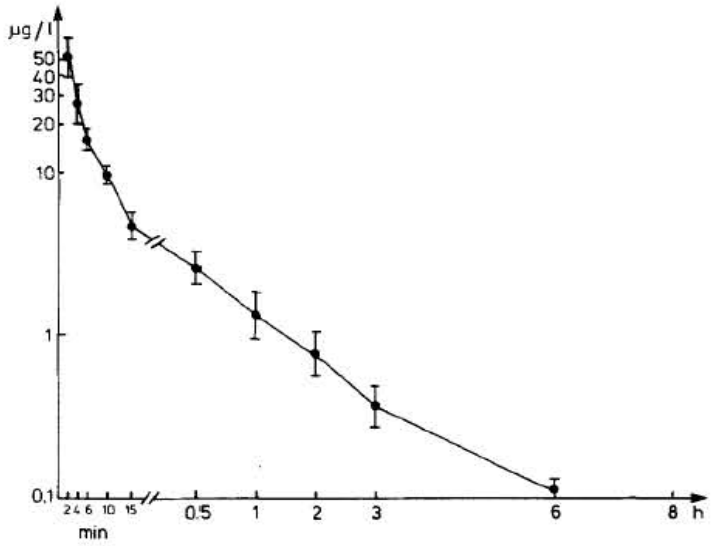


Fig 01: Plasma concentrations of glycopyrrolate after an intravenous injection (6 µ/kg)

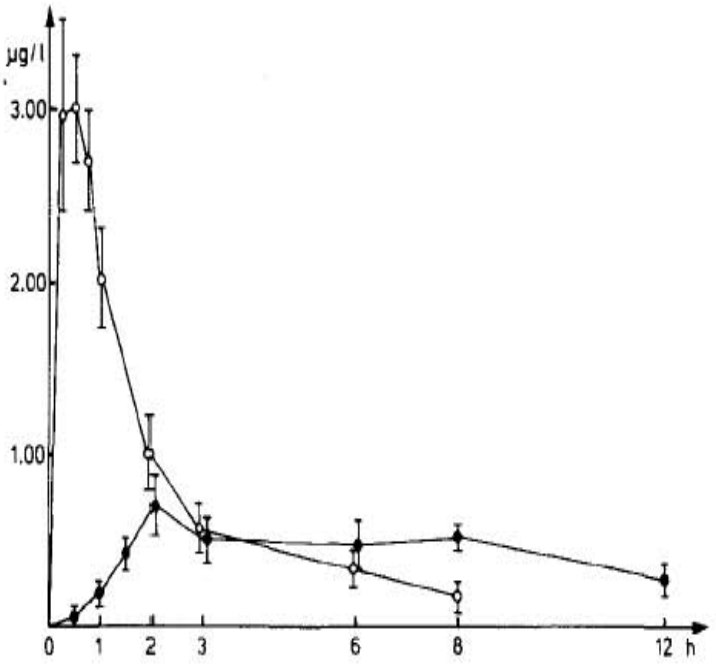


Fig 02: Plasma concentrations of glycopyrrolate following a single oral (4 mg; ●----●) and intramuscular (8 µg/kg; 0---0).

2.5.3.3.1 Absorption

The applicant has performed a bioequivalence study comparing Glycopyrronium Bromide 2mg Tablets with the reference product formulation (Cuvposa) in a bioequivalence study in healthy subjects under fasting conditions (study no. 934-19). The mean Cmax was 642.9620 pg./mL and 581.0435 pg./mL for test and reference formulation respectively. Mean AUC0-t and AUC0-inf were 3221.2630 pg.*hr/mL and 3349.5189 pg.*hr/mL respectively for test formulation and 3065.6417 pg.*hr/mL and 3202.5926 pg.*hr/mL respectively for reference formulation.

Glycopyrronium Bromide is poorly absorbed from the gastrointestinal tract. Mean peak concentration reported is 0.318 ng / mL at 3.1 hours following oral administration in adult population. The peak plasma concentration of Glycopyrrolate oral solution was 23% lower than oral tablets when administered to fasting adults. Food decreases the mean time to peak concentrations (3.1 to 2.6 hours) and mean peak concentration (0.318 to 0.084 ng / mL). (Glycopyrrolate Oral Solution, Drug Bulletin, 2011; Glycopyrrolate Oral Solution, FDA Review, 2010 and Garnock-Jones Karly P. et al 2012).

In pharmacokinetic studies conducted in children and adults, Glycopyrrolate has been shown to be poorly absorbed after oral administration, with a range of bioavailability from 01% – 20 %. Food effect studies indicate that the mean C_{max} under fed high fat meal conditions is about 74% lower than the C_{max} observed under fasting conditions. (Buck Marcia L. et al 2010).

The presence of high fat food reduces the oral bioavailability of Glycopyrrolate oral solution if taken shortly after a meal. When administered under fed conditions, the mean C_{max} and $AUC_{0-\infty}$ were both decreased by 75% compared with fasting conditions; median and mean T_{max} and T_{half} were not significantly altered. Glycopyrrolate should therefore be administered $\geq$1 hour before or $\geq$2 hours after meals. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Garnock-Jones Karly P. et al 2012).

Analysis of population pharmacokinetic data from normal adults and children with cerebral palsy associated chronic moderate to severe drooling failed to demonstrate linear pharmacokinetics across the dose range. In the same analysis, population estimates of the apparent oral clearance (scaled by weight in children and adults) ranged from 5.28 - 38.95 L/hr/kg for healthy adults and 8.07 - 25.65 L/hr/kg for patients with cerebral palsy, a reflection of the low and highly variable oral bioavailability of glycopyrrolate. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018)

2.5.3.3.2 Distribution

Glycopyrrolate does not penetrate the blood-brain or placental barrier in significant amounts and consequently seldom causes central nervous system or neonatal toxicity. [Kanto J. et al 1988, Zeller Robert S. et al 2012(a) and Zeller Robert S. et al 2012(b)].

In adults aged 60-75 years, the volume of distribution was lower (0.42 L/kg). (Buck Marcia L. et al 2010; CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Glycopyrrolate Oral Solution, Drug Bulletin, 2011).

2.5.3.3.3 Metabolism

Kaltiala et al studied the fate of intravenous ^{3}H-glycopyrrolate in six patients by determining serum levels and the biliary and urinary excretion of radioactivity. More than 90% of total radioactivity disappeared from serum in 5 min and almost all in 30 min. The highest activity in bile was detected between 30 and 60 min after injection and a low measurable activity up to 48 h. As with bile, the highest radioactivity in the urine was found in the first samples (0-3 h) and after 6 h drug excretion appeared to be insignificant, in 48 h 85% of the total radioactivity was excreted into the urine. In both bile and urine, over 80% of the radioactivity corresponded to unchanged glycopyrrolate. [(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018; Kaltiala E. et al 1974, Mirakhur R. K. et al 1983 and Kanto J. et al 1988]

2.5.3.3.4 Elimination

Approximately 65%-80% of an intravenous glycopyrrolate dose was eliminated unchanged in urine in adults. (Buck Marcia L. et al 2010) In two studies, after IV administration to pediatric

patients ages 1-14 years, mean clearance values ranged from 1.01- 1.41 L/kg/hr (range 0.32 - 2.22 L/kg/hr). In adults, IV clearance values were 0.54 ± 0.14 L/kg/hr. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Glycopyrrolate Oral Solution, Drug Bulletin, 2011).

Glycopyrronium Bromide is excreted largely unchanged in the urine. The remaining portion is believed to be metabolized and excreted in the bile. (Buck Marcia L. et al 2010).

Mean elimination half-life following Glycopyrrolate after Oral Solution is approximately 03 hours. (Garnock-Jones Karly P. et al 2012). The drug is primarily renally excreted (> 65%) with some bile and minimal hepatic excretion. (Glycopyrrolate Oral Solution, Drug Bulletin, 2011).

Murray et al. determined plasma levels of glycopyrronium bromide up to 50 min following a single i.v. dose of 0.3 mg. The fast disappearance of glycopyrrolate from the circulation and its rapid excretion into urine and bile are in accordance with its short antisecretory action of around 2 – 3 hours. The apparent high concentrations in the bile suggest a spasmolytic effect on the bile ducts, associated with a reduction in the spasmolytic and analgesic drugs needed. (Kanto J. et al 1988)

2.5.3.3.5 Pharmacokinetics in Special Populations

2.5.3.3.5.1 Pharmacokinetics in Elderly

Glycopyrrolate pharmacokinetics have not been characterized in the elderly. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

2.5.3.3.5.2 Pharmacokinetics in Paediatric Population

Glycopyrrolate is widely distributed in children, with an average volume of distribution of 1.3 - 1.8 L / kg significantly greater than that reported in adults (0.42 L / kg). The clearance of Glycopyrrolate appears to be more rapid in children. (Buck Marcia L. et al 2010).

C_{max} of the oral solution was 23 % lower than the marketed oral tablet. Mean T_{max} was 3.1 hours for the oral solution while mean plasma t½ was 3 hours and clearance ranged from 0.6 to 1.43 L / kg / h. (Eiland Lea S. et al 2012).

Pharmacokinetics and bioavailability of glycopyrrolate was evaluated following a single oral (50 µg/kg) and intravenous (5 µg/kg) administration in 06 healthy children (age 7 – 14 years) operated twice. Blood samples were collected at pre-dose and at 2, 4, 6, 10, 15, 30, 60, 120, 180, 240, 360 and 480 min. after intravenous administration and at 30, 60, 120, 180, 360, 480 and 720 min. after oral administration of the drug. The basic pharmacokinetic results are tabulated below:

Table 12: Pharmacokinetic Parameters of Glycopyrrolate in Children (oral)

C_{max} (µg/L)	T_{max} (min)	$AUC_{0-\infty}$ (µg/L. min)	F (%)
0.37 (0.19 - [illegible])	90 (30 - 480)	106.6 (38.5 - 278.7)	3.3 (1.3 - 13.3)

Table 13: Pharmacokinetic Parameters of Glycopyrrolate in Children (intravenous)

$AUC_{0-\infty}$ (µg/L. min)	$T_{½}$ (min)	Vss (L/kg)	Cl (l/kg/hr)
276.3 (210.2 – 502.8)	139 (73 – 239)	1.37 (0.75 – 2.64)	1.09 (0.60 – 1.43)

After intravenous injection glycopyrrolate disappeared rapidly from the circulation with elimination half-life (median) of 139 min. Oral administration of glycopyrrolate produced very low plasma concentrations lasting up to 12 hours accompanied by considerable interindividual alterations in kinetic parameters. Bioavailability of glycopyrrolate after oral dose of 50 µg/ kg was only 3.3 % (1.3 - 13.3).

(Rautakorpi P. et al 1998).

Pharmacokinetics of glycopyrrolate was evaluated following a single intravenous dose of 5 µg/kg administered to 26 children before induction of anesthesia. Patients were assigned to 1 of 3 groups: under 1 year of age (Group 1, n=8), between 1 and 3 years of age (Group 2, n=7) and over 3 years of age (Group 3, n=11). The plasma concentrations of glycopyrrolate are shown in figure and parameters are in table below.

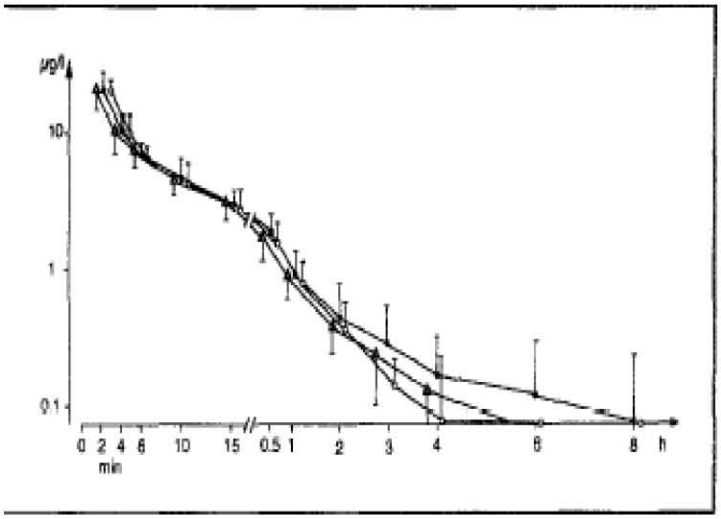


Fig 03: Plasma concentrations of glycopyrrolate after an intravenous injection (5 µg/kg)

Table 14: Basic Pharmacokinetic Characteristics

	$AUC_{0-\infty}$ (µg/1 min)	$T_{1/2}$ (min)	Vss (L/kg)	CL (L/kg/hr)
Group 1	297.4 (169.1 to 926.6)	129.5 (28.0 to 634.1)	1.83 (1.70 to 3.87)	1.01 (0.32 to 1.85)
Group 2	213.0 (134.9 to 308.8)	46.7 (43.4 to 74.1)	1.31 (0.80 to1.71)	1.41 (0.97 to 2.22)
Group 3	280.4 (167.5 to 488.8)	99.2 (39.2 to 371.3)	1.45 (0.76 to 3.56)	1.07 (0.61 to 1.79)

Glycopyrrolate disappeared from plasma very rapidly. Steady state volume of distribution (Vss) appeared to be higher and clearance (Cl) lower in Group 1 when compared with Groups 2 and 3, but the differences were not statistically significant. The only significant difference was the shortened elimination half-life ($t_{½}$) in Group 2. Age appears to have no prominent effect on the pharmacokinetics of glycopyrrolate in children. Interestingly, there were great interindividual differences in pharmacokinetic parameters in the youngest group (Group 1).

(Rautakorpi Pirkka et al 1994)

2.5.3.3.5.3 Pharmacokinetics in Patients with Renal Impairment

The clearance of Glycopyrrolate in patients with renal dysfunction is significantly impaired and delayed as compared to healthy subjects. (Buck Marcia L. et al 2010).

Kirvela et al studied the pharmacokinetics of glycopyrronium in 11 uraemic patients undergoing cadaveric renal transplantation and in seven ASA I control patients undergoing general surgery. Glycopyrronium 4 µg/kg was given i.v. before induction of anaesthesia. Blood and urine samples were collected for up to 24 h for measurement of glycopyrronium concentrations. Volume of distribution in the elimination phase (Vβ) was similar in both groups, the elimination half-life (T½β) was longer, area under the plasma concentration-time curve (AUC) larger and plasma clearance (Cl) smaller in the uraemic patients. In 3 h, mean 0.7% (range 0-3) and 50% (21-82) of glycopyrronium was excreted in the urine in the uraemic and healthy patients, respectively. The 24-h renal excretion was 7% (0-25) in uraemic and 65% (30-99) in control patients. In conclusion, the elimination of glycopyrronium is severely impaired and prolonged in uraemic patients. (Kirvela et al 1993)

2.5.3.3.5.4 Pharmacokinetics in Patients with Hepatic Impairment

The pharmacokinetics of glycopyrrolate has not been evaluated in patients with hepatic impairment. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Garnock-Jones Karly P. et al 2012).

2.5.3.3.5.5 Pharmacokinetics in Different Genders

Patient with different genders appeared to have no effect on the pharmacokinetics of glycopyrrolate as studied in population pharmacokinetic analyses. (Garnock-Jones Karly P. et al 2012).

Population pharmacokinetic evaluation of adults and children administered oral glycopyrrolate identified no effect of gender on glycopyrrolate clearance or systemic exposure. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

2.5.3.3.5.6 Pharmacokinetics in Different Race

The pharmacokinetics of glycopyrrolate by race has not been characterized. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

2.5.3.3.5.7 Pharmacokinetics in Patients

Cerebral Palsy Patients

Population analyses of pharmacokinetic data estimated that apparent oral clearance ranged from 8.07 to 25.65 L/h/kg in patients with cerebral palsy, reflecting glycopyrrolate relatively low and highly variable oral bioavailability. (Garnock-Jones Karly P. et al 2012).

Surgical Patients

Pharmacokinetics of glycopyrrolate was studied in humans by determining the plasma concentrations and the renal excretion in three gynaecological surgical patients, who received 8 µg/kg of glycopyrrolate as a premedication intramuscularly. A very rapid absorption was found with a mean maximum plasma concentration of 14.26 (range 12.02-16.97) µg / L and mean T_{max} of 13.3 (range 1 & 15) minutes and almost 50%of the dose administered was excreted into the urine within 3 hr. (Kaila T. et al 1990)

Pharmacokinetics of glycopyrronium 6 µg/kg was studied after intramuscular administration in eight caesarean section patients. A very rapid absorption rate was found, with a mean maximum plasma concentration (Cmax) of 6.3 (SD 1.5) ng/ml and mean time to Cmax (Tmax) of 10.0 (3.8) minutes. The respective AUC value from 0 to 8 hours was 5.61 (1.27) hours. ng/ml and the elimination half-life were 33.4 (1.9) minutes. The estimated systemic clearance was 1.12 (0.23) (litres/hour)/kg. Almost half of drug (48.3%) was excreted into the urine within 3 hours. There were no measurable levels of glycopyrronium in the lumbar cerebrospinal fluid (CSF) after 60 minutes of drug injection. The concentrations of glycopyrronium in the umbilical venous [0.28 (0.25) ng/ml] and in the umbilical arterial [0.18 (0.11) ng/ml] plasma after 86 minutes of drug injection were low and clinically insignificant, as was the case in the amniotic fluid [0.15 (0.08) ng/ml]. In conclusion, the absorption of

glycopyrronium after intramuscular administration is very rapid and the elimination half-life is short. [Ali-Melkkila et al 1990(a)]

Ali-Melkkila et al determine the pharmacokinetics of glycopyrronium following a single intramuscular injection of 8 µg/kg in nine surgical patients. Pharmacokinetic parameters based on plasma concentrations are given in table below:

Table 15: Pharmacokinetics Parameters in 09 Gynaecological patients receiving glycopyrronium 8 µg/kg

	Cmax ($ng\ ml^{-1}$)	tmax (min)	$AUC_{0-6\ h}$ ($h\ ng\ ml^{-1}$)	$T_{\frac{1}{2}}$ (min)	Cl (litre $h^{-1}\ kg^{-1}$)
Mean	15.79	16.11	14.11	75.4	0.58
SD	(10.76)	(8.21)	(11.57)	(14.91)	(0.18)

Rapid absorption was found, with a mean peak plasma concentration after 16.1 min and mean elimination half-life of 75.4 min. Almost half (49.3%) of the drug was excreted in pharmacologically active form in the urine within 3 h. There was no measurable glycopyrronium in lumbar cerebrospinal fluid samples (n = 9) taken 40 min after administration of drug. [Ali-Melkkila et al 1990(b)]

2.5.3.4 Pharmacokinetics and Pharmacodynamic Relationship

Following a single oral (50 µg/kg) administration of Glycopyrrolate in 06 healthy children aged between 7 – 14 years, very low plasma concentrations of glycopyrrolate lasting up to 12 hours were reported accompanied by considerable interindividual alterations in kinetic parameters with mean Cmax around 0.37 µg/l. No significant changes in heart rate or arterial were noted following oral administration of the drug. While in another pharmacokinetic – pharmacodynamic study Cartabuke et al 1991 reported that oral glycopyrrolate (50 µg/kg) has only minor effects on heart rate. (Rautakorpi P. et al 1998).

After intravenous injection of glycopyrrolate (5 µg/kg) in 06 healthy children aged between 7 – 14 years, only one patient had a measurable level of glycopyrrolate after 8 hr. and in most patient's plasma concentrations were under 10 µg/l (Cmax) after 4 min. There were no significant changes in heart rate or arterial blood pressure after intravenous administration of the drug. (Rautakorpi P. et al 1998).

Following intravenous administration of glycopyrrolate to 26 healthy children, no significant heart rate alterations were reported at the dose of 5 µg/kg. (Rautakorpi Pirkka et al 1994)

Penttilla Jani et al conducted a study to evaluate the pharmacokinetic-pharmacodynamic model for the anticholinergic effect of glycopyrrolate in 08 healthy male volunteers. The effect of 2-hour glycopyrrolate intravenous infusion (5 µg/kg/hr) on the mean R-R interval (RRI) and the Hayano index of the high frequency variability of RRI (HF CCV) was modelled using an effect compartment, sigmoidal Emax model, with the individual PK parameters. Modelling of the HF CCV data yielded the following mean (± SD) estimates: concentration at 50% of Emax (EC50), 2.46 ± 0.58 ng / mL, equilibration half-time, 42.5 ± 7.7 min and sigmoidicity factor, 7.26 ± 2.82. The corresponding values for RRI data were 2.79 ± 0.52 ng/ml, 58.3 ± 17.2 min and 4.75 ± 1.56. The measured arterial drug concentration approached the targeted steady state side effect concentration in most of the subjects, while the observed effect appeared to surpass the target levels. (Penttilla Jani et al 2001)

Extrapolation of PK-PD data between paediatric and adult age groups

In a study done by Ali-Melkkilä et al (1989) the PK-PD correlation of glycopyrronium and reproducible radio receptor assay (RRA) was used to study the pk /pd sensitive comparison between intramuscular and oral use of glycopyrronium. After oral drug intake, 4 mg (n = 6), an apparently low and variable gastrointestinal absorption was found (t_{max} = 300.0 ± 197.2 min, C_{max} = 0.76 ± 0.35 µg/1), thus indicating that the oral route of drug administration is of no value as a routine premedication. The correlation between the plasma concentration of glycopyrrolate and the drug effects appears to be variable. Furthermore, literature data suggest that treatment with glycopyrronium should begin at low doses and titrated every 5-7 days based on response and tolerability to a maximum of 2.4 mg per dose. In pharmacokinetic studies conducted in children and adults, glycopyrrolate has been shown to be poorly absorbed after oral administration, with a range of bioavailability from 1-20%. There is considerable variation in absorption among patients. Administration with a high fat meal further reduces absorption of glycopyrrolate oral solution by approximately 74%. Glycopyrrolate is widely distributed in children, with an average volume of distribution of 1.3-1.8 L/kg, significantly greater than that reported in adults (0.42 L/kg). The clearance of glycopyrrolate appears to be more rapid in children. In two paediatric studies using intravenous glycopyrrolate, the average clearance was 1-1.4 L/kg/hr, with a range of 0.3-2.2 L/kg/hr. In adults, the average rate of clearance is 0.54 L/kg/hr. (Ali-Melkkilä et al 1989, CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018)

The guide to treatment remains response to treatment in both age groups. No increased dosing has been proposed for the adult patient and essentially the maximum daily dose remains the same for a child above 30 kg and an adult. In the Arbouw et al study 23 patients with Parkinson disease were studied over a 4-week period using oral glycopyrrolate 1mg and 3 times daily. The study concluded that Oral glycopyrrolate 1 mg 3 times daily is an effective and safe therapy for sialorrhea in Parkinson disease. The study highlights that glycopyrrolate dosage of 1 mg 3 times daily is relatively modest. This dosage was based on reports as well as pilot observations in some of their own outpatients. A maximum dosage of 8 mg/d had been advised, which may lead to an even greater reduction of sialorrhea. However, increase of

glycopyrrolate dose also may lead to an increase of adverse events. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018, Arbouw M. E. L. et al 2010)

The dose for adults is based on the same dose proposed for children with a body weight of over 30kg. Mier et al. conducted a randomized, placebo-controlled, double-blind, crossover, dose-ranging study with 39 patients aged 4 – 19 years. The 2 oral glycopyrrolate dosage regimens were based on weight: patients < 30 kg initially received 0.6 mg 3 times daily, with weekly increases to 1.2, 1.8, and 2.4 mg 3 times daily; patients > 30 kg started at 1.2 mg 3 times daily, with weekly increases to 1.8, 2.4, and 3 mg 3 times daily, if tolerated. All 27 children who completed the study demonstrated improvement in drooling. The mean baseline drooling score improved with glycopyrrolate from 7.52 to a maximum mean score of 1.85. Drooling scores improved with increasing dose in a linear manner. (Mier R. J. et al 2000)

Proakis et al 1978 discuss the penetration of glycopyrrolate and atropine across the blood-brain and placental barriers in dogs. A study shows that glycopyrronium is a selective peripheral anticholinergic agent and thus resistant to penetration across the blood brain barrier and placental barriers. (Proakis A. G. et al 1978)

2.5.3.5 Drug Interactions

2.5.3.5.1 Pharmacokinetic Interactions

Coadministration of glycopyrrolate and certain drugs in delayed- or controlled-release formulations may result in altered release of the latter, as glycopyrrolate reduces gastrointestinal transit time. Gastrointestinal passage of potassium chloride may be arrested or delayed when coadministered with glycopyrrolate.

Drugs whose plasma levels may be increased by Glycopyrrolate:

- Atenolol's bioavailability may be increased with coadministration of glycopyrrolate.
- Metformin plasma levels may be elevated with coadministration of glycopyrrolate, increasing metformin's pharmacologic and toxic effects.
- Glycopyrrolate oral solution increases levels of digoxin when administered in combination with Digoxin slow dissolution oral tablets.

Drugs whose plasma levels may be decreased by Glycopyrrolate:

Coadministration of glycopyrrolate may result in decreased levels of certain drugs.

- Haloperidol's serum level may be decreased when coadministered with glycopyrrolate, resulting in worsening of schizophrenic symptoms, and development of tardive dyskinesia. Closely monitor patients if coadministration cannot be avoided.
- Levodopa's therapeutic effect may be reduced with glycopyrrolate administration. Consider increasing the dose of levodopa.

(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018; Cuvposa, Shionogi Inc., 2012; Buck Marcia L. et al 2010; Eiland Lea S. et al 2012 and Garnock-Jones Karly P. et al 2012).

Lignocaine

Watanabe et al studied the effect of glycopyrronium on absorption of topical lignocaine in 10 healthy, non-smoking volunteers. Lignocaine 100 mg was sprayed on the oral mucosa 15 min after intravenous administration of glycopyrronium 4 µg kg or normal saline. The mean (SD) peak plasma lignocaine concentration was 0.57 (0.29) µg/ml after glycopyrronium and 0.31 (0.10) µg/ml after saline and were attained in 17 min (range 10-40 min) and 29 min (range 8-40 min). respectively. Pre-treatment with glycopyrronium enhanced absorption the analgesic action of topically administered lignocaine. (Watanabe H. et al 1993)

Ethambutol

Glycopyrronium delayed the ethambutol absorption in healthy volunteers as indicated by lowered serum ethambutol levels during the first few hours after its administration. (Mattila M. J. et al 1978)

Cimetidine

In an open-label, two-period, two-sequence, crossover study, 20 healthy subjects received 2 treatments. In treatment A, a single dose of 100 µg glycopyrrolate was inhaled. In treatment B, cimetidine 800 mg b.i.d. p.o. was given and a single 100 µg inhaled dose of glycopyrrolate on day 4. Plasma concentrations and urinary excretion of glycopyrrolate were determined up to 72 h post glycopyrrolate dose. Inhalation of glycopyrrolate in the presence of cimetidine resulted in an increase in total systemic exposure of glycopyrrolate by 22%. This exposure increase correlated with a slight decrease of 23% in CL. C_{max} was not affected. Both treatments were safe and well tolerated without any deaths or severe adverse events. Therefore, it was concluded that glycopyrrolate may be co-administered with cimetidine or other inhibitors of the organic cation transport. (Dumitras S. et al 2013).

2.5.3.5.2 Pharmacodynamic Interactions

Drugs Affected by Reduced GI Transit Time:

Glycopyrrolate reduces GI transit time, which may result in altered release of certain drugs when formulated in delayed or controlled release dosage forms.

- The passage of potassium chloride tablets through the GI tract may be arrested or delayed with coadministration of glycopyrrolate.

- Digoxin administered as slow dissolution oral tablets may have enhanced action when administered with glycopyrrolate. Monitor patients receiving slow dissolution digoxin for increased action if glycopyrrolate is co-administered regularly. Consider the use of other oral dosage forms of digoxin (e.g., elixir or capsules).

The effects of glycopyrrolate may be intensified by administration with other anticholinergics, including amantadine, phenothiazines, or tricyclic antidepressants.

(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Buck Marcia L. et al 2010).

Amantadine

Coadministration of glycopyrrolate oral solution and amantadine may result in increased anticholinergic effects of glycopyrrolate and hence the glycopyrrolate dose may need to be decreased in patients receiving both these drugs. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018; Eiland Lea S. et al 2012 and Garnock-Jones Karly P. et al 2012).

Lignocaine

Watanabe et al studied the effect of glycopyrronium on the anaesthetic action of topical lignocaine in 10 healthy, non-smoking volunteers. Lignocaine 100 mg was sprayed on the oral mucosa 15 min after intravenous administration of glycopyrronium 4 μg kg or normal saline. Glycopyrronium decreased the mean analgesia score from 2 to 0.1 (2 = baseline; 0 = anaesthesia) at 4 min compared with a change from 2 to 0.5 after normal saline. All scores returned to baseline by 40 min and 20 min in the glycopyrronium and control groups, respectively. Pre-treatment with glycopyrronium prolonged the analgesic action of topically administered lignocaine. (Watanabe H. et al 1993)

Drug-drug interactions of a varying degree with several drugs are known with anticholinergic agents in general. Glycopyrronium bromide is an anticholinergic compound (with a quaternary structure), hence similar drug-drug interactions are expected. Specifically, co-administration of other anti-cholinergics is cautioned against as they may exacerbate the adverse effects of glycopyrronium bromide. Several drugs used as antipsychotics, antidepressants and anti-parkinson drugs fall in this class of drugs. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018)

The slower gastrointestinal time produced by glycopyrrolate may increase the risk for hyperkalemia from sustained-release potassium chloride products and reduce the effectiveness of digoxin. Glycopyrrolate may increase plasma levels of atenolol or metformin if given concomitantly with these agents. Administration with glycopyrrolate may reduce plasma levels of haloperidol or levodopa. (Buck Marcia L. et al 2010)

In general, there are total of 190 drugs are known to interact with glycopyrrolate. Out of these the 04 major drug interactions are with topiramate, potassium chloride, potassium citrate & with zonisamide. Rest with other 166 drugs which have moderate drug-drug interactions are as follows:

Table 16: Drugs which has moderate drug-drug interactions are as follows

• Abobotulinumtoxina • Acebutolol • Acetylcholine ophthalmic • Aclidinium • Acrivastine • Amantadine • Ambenonium • Amitriptyline • Amoxapine • Arbutamine • Aripiprazole • Asenapine • Atenolol • Atropine • Azatadine •	• Belladonna • Benztropine • Betaxolol • Bethanechol • Biperiden • Bisoprolol • Brexpiprazole • Brompheniramine • Buprenorphine • Butorphanol •	• Carbachol ophthalmic • Carbinoxamine • Cariprazine • Carteolol • Carvedilol • Cevimeline • Chlorcyclizine • Chlorpheniramine • Chlorpromazine • Cisapride • Clemastine • Clidinium • Clomipramine • Clozapine • Codeine • Cyclizine • Cyclobenzaprine • Cyproheptadine
• Darifenacin • Demecarium bromide ophthalmic • Desipramine • Dexbrompheniramine • Dexchlorpheniramine • Dezocine • Dicyclomine • Dimenhydrinate • Diphenhydramine • Disopyramide • Donepezil • Doxepin • Doxepin topical • Doxylamine	• Echothiophate iodide ophthalmic • Edrophonium • Eluxadoline • Ethanol •	• Fentanyl • Fesoterodine • Flavoxate • Fluphenazine
• Galantamine • Glycopyrronium topical • Guanidine	• Haloperidol • Hydrocodone • Hydromorphone • Hydroxyzine • Hyoscyamine	• Iloperidone • Imipramine • Incobotulinumtoxina • Ipratropium • Isoflurophate

	•	ophthalmic
• Ketoconazole •	• Labetalol • Levodopa • Levomethadyl acetate • Levorphanol • Loperamide • Loxapine • Lurasidone •	• Maprotiline • Meclizine • Memantine • Mepenzolate • Meperidine • Mesoridazine • Methadone • Methdilazine • Methotrimeprazine • Methscopolamine • Metoclopramide • Metoprolol • Molindone • Morphine • Morphine liposomal
• Nadolol • Nalbuphine • Nebivolol • Neostigmine • Nortriptyline •	• Olanzapine • Onabotulinumtoxina • Opium • Orphenadrine • Oxybutynin • Oxycodone • Oxymorphone •	• Paliperidone • Penbutolol • Pentazocine • Perphenazine • Phenindamine • Phenylephrine • Phenylephrine ophthalmic • Physostigmine • Physostigmine ophthalmic • Pilocarpine • Pilocarpine ophthalmic • Pimozide • Pindolol • Pramlintide • Procainamide • Prochlorperazine • Procyclidine • Promazine • Promethazine • Propantheline • Propiomazine • Propoxyphene • Propranolol • Protriptyline • Prucalopride • Pyridostigmine • Pyrilamine
• Quetiapine • Quinidine	• Revefenacin • Rimabotulinumtoxinb	• Scopolamine • Solifenacin

	• Risperidone • Rivastigmine	• Sotalol •
• Tacrine • Thiethylperazine • Thioridazine • Thiothixene • Timolol • Tiotropium • Tolterodine • Trifluoperazine • Triflupromazine • Trihexyphenidyl • Trimeprazine • Trimipramine • Tripelennamine • Triprolidine • Trospium	• Umeclidinium •	• Ziprasidone •

2.5.3.6 Posology

<u>The recommended dosage in the applicant SPC is as follows:</u>

Glycopyrronium bromide tablets should be prescribed by physicians experienced in the treatment of patients with neurological disorders.

The dosing schedule for Glycopyrronium bromide tablets is based on the weight of the child with the initial dosing of 0.02 mg/kg to be given orally three times daily and titrate in increments of 0.02 mg/kg every 5-7 days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily not to exceed 1.5-3 mg per dose based upon weight. For greater detail, see Table 14.

During the four-week titration period, dosing can be increased with the recommended dose titration schedule while ensuring that the anticholinergic adverse events are tolerable. Prior to each increase in dose, review the tolerability of the current dose level with the patient's caregiver.

Younger children may be more susceptible to adverse events and this should be kept in mind when dose adjustments are carried out.
(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018, Mier R. J. et al 2000)

Table 17: Dosing tables for children and adolescents aged 3 years and older

Weight	**Dose level 1**	**Dose level 2**	**Dose level 3**	**Dose level 4**	**Dose level 5**
Kg	**(~0.02 mg/kg)**	**(~0.04 mg/kg)**	**(~0.06 mg/kg)**	**(~0.08 mg/kg)**	**(~0.1 mg/kg)**
13-17	0.3mg	0.6mg	0.9mg	1.2mg	1.5mg
18-22	0.4mg	0.8mg	1.2mg	1.6mg	2.0mg

23-27	0.5mg	1.0mg	1.5mg	2.0mg	2.5mg
28-32	0.6mg	1.2mg	1.8mg	2.4mg	3.0mg
33-37	0.7mg	1.4mg	2.1mg	2.8mg	3.0mg
38-42	0.8mg	1.6mg	2.4mg	3.0mg	3.0mg
43-47	0.9mg	1.8mg	2.7mg	3.0mg	3.0mg
>48	1.0mg	2.0mg	3.0mg	3.0mg	3.0mg

The tablet product may not be suitable for certain dose levels.

Dose titration should be continued until efficacy is balanced with undesirable effects and amended up or down as appropriate, to a maximum recommended dosage not exceeding 9 mg on daily basis. (Mier R. J. et al 2000)

Paediatric population – Children and adolescents aged 3 years and older with body weight of over 30 kg and adults (Mier R. J. et al 2000) Glycopyrronium bromide tablets are not recommended in children aged below 3 years in the symptomatic treatment of sialorrhoea (chronic pathological drooling). (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018)

Elderly population

The elderly has a longer elimination half-life and reduced medicinal product clearance as well as limited data to support efficacy in short-term use. As such glycopyrronium bromide tablets should not be used in patients over the age of 65 years. (Buck Marcia L. et al 2010)

Renal Impairment

For patients with renal impairment the elimination of glycopyrronium is likely to be impaired.

Glycopyrronium bromide tablet is contraindicated for patients with severe renal impairment.

For patients with Mild to moderate renal impairment (eGFR <90 - ⩾30 ml/min/1.73m^2) doses should be reduced by 30%, therefore the tablet product is unsuitable for patients with renal impairment and other pharmaceutical forms should be used. (Buck Marcia L. et al 2010)

Hepatic impairment

Clinical studies have not been conducted in patients with hepatic impairment. Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion and hepatic impairment is not thought to result in a clinically relevant increase in systemic exposure of glycopyrronium.

High fat food should be avoided. The presence of high fat food reduces the oral bioavailability of Glycopyrronium Bromide if given shortly after a meal. Therefore, it should be given at least one hour before or two hours after meals. If the patient's specific needs determine that co-administration with food is required, dosing of the medicinal product should be consistently performed during food intake. (Glycopyrrolate Oral Solution, FDA Review, 2010 and Garnock-Jones Karly P. et al 2012).

Method of administration

For oral administration only.

2.5.4 OVERVIEW OF EFFICACY

Glycopyrrolate brings clinical value to the treatment of chronic severe drooling, however it may offer some convenience over other options because of dosing flexibility for individual patients. (Cuvposa, Therapeutic Class Review, 2011).

Studies involving Paediatric Patients

The literatures available in public domain describe the use of glycopyrrolate for drooling in two principal clinical situations: in children, mainly with cerebral palsy, who have poor saliva control, and in adults with neurological conditions such as Parkinson Disease. Additionally, there are reports of the use of glycopyrrolate in two further clinical situations. Firstly, there is a report of the use of nebulized glycopyrrolate for drooling in motor neuron disease. Secondly, it has been used in clozapine induced sialorrhea. (Reddihough D. S. et al 2011).

Short Term Studies (8-week trial)

Efficacy of Glycopyrrolate oral solution (Cuvposa^{TM}) was evaluated in treatment of drooling associated with cerebral palsy and other neurologic conditions in 38 pediatric patients in a randomized blinded placebo-controlled trial. Patients were dosed with Glycopyrrolate (n = 20) 0.02 – 0.1 mg / kg three times a day or matching placebo (n = 18) and was titrated according to schedule over a 4-week period to optimal response, with a maximum dose of 0.1 mg / kg or 3 mg three times a day, whichever was less. Since high-fat foods reduce the oral bioavailability of glycopyrrolate oral solution administered shortly after a meal, the investigational products were administered at least 1 hour before or 2 hours after meals at 7 – 8 am, 1 – 2 pm and 7 – 8 pm. At week 8, 14 of 19 patients (73.7%) in the glycopyrrolate oral solution group and three of 17 (17.6%) in the placebo group exhibited at least a 3-point improvement in modified Teacher's Drooling Scale (mTDS) score with improvements starting 2 weeks after treatment initiation. Mean improvements in mTDS at week 8 were significantly greater in the Glycopyrrolate than in the placebo group (3.94 ± 1.95 vs 0.71 ± 2.14 points). Results indicate the superiority of Glycopyrrolate oral solution over placebo in controlling drooling associated with neurologic conditions in pediatric patients. In addition, 84 % of physicians and 100 % of parents / caregivers regarded glycopyrrolate as worthwhile compared with 41 % and 56 % respectively for placebo. [Garnock-Jones Karly P. et al 2012, PR Newswire, Shionogiinc, US,2012 and Zeller Robert S. et al 2012(a)].

A multicenter, randomized, double-blind, placebo-controlled study was conducted in children with chronic sialorrhea associated with an underlying neurologic condition. A total of 38 patients between the ages of 3 and 23 years were enrolled into the 8-week study receiving either Glycopyrrolate oral solution (Cuvposa^{TM}) at a dose of 0.02 mg / kg or placebo three times daily. The dose was titrated by increments of 0.02 mg / kg every 5 to 7 days based on clinical responses. The maximum dose was 0.1 mg / kg or 3 mg given three times daily. Patients were considered responders if there was at least a 3-point reduction in mean daily

mTDS (Modified Teacher's Drooling Scale) score from baseline to week 8. At week 8, 75% of the children given Glycopyrrolate oral solution were considered responders compared to only 11% of the patients in the placebo group concluding superiority of Glycopyrrolate. (Buck Marcia L. et al 2010 and Glycopyrrolate Oral Solution, Drug Bulletin, 2011).

Long Term Studies (24-week trial)

Efficacy of Glycopyrrolate oral solution (Cuvposa™) was assessed in 137 pediatric patients 3 – 18 years with chronic moderate to severe drooling associated with cerebral palsy and other neurologic conditions in a 24-week multicenter, open-label trial. Patients 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. At 24 weeks, 52.3 % of patients were responders, with at least a three-point decrease in modified Teacher's Drooling Scale from baseline, with 83.5 % of parents / caregivers and 85.8 % of investigators rating oral Glycopyrrolate solution as being worthwhile concluding the effectivity of Glycopyrrolate oral solution in drooling pediatric patients. Improvements in the extent of drooling were also observed using the visual analog scale assessment. The mean visual analog score was reduced from 6.56 at baseline to 3.21 at 24 weeks. [Eiland Lea S. et al 2012; Garnock-Jones Karly P. et al 2012, PR Newswire, Shionogi inc, US, 2012 and Zeller Robert S. et al 2012(b)].

Comparative Trials

Parr et al evaluated the efficacy of hyoscine patch or glycopyrronium liquid in treatment of drooling in children with neurodisability using a multicentre, single-blind, randomised controlled trial. Ninety children with neurodisability who had never received medication for drooling (median age 4 years) were enrolled and 85 started treatment: 47 hyoscine, 38 glycopyrroniumMedication was increased weekly from week-1 to week-4 to the dose needed to stop drooling or to the maximum allowed dose or to the maximum associated with tolerable adverse effects. Thereafter, participants remained on the week-4 medication dose for 8 weeks. Children randomised to hyoscine received regime: week-1: ¼ patch; week-2: ½ patch; week-3: ¾ patch; week-4: full patch. Children randomised to glycopyrronium liquid received three doses per day: week-1: 40 µg/kg/per dose; week-2: 60 µg/kg/per dose; week-3: 80 µg/kg/ per dose; week-4: 100 µg/kg/per dose to a maximum 2 mg per dose. Both medications yielded clinically and statistically significant reductions in mean Drooling Impact Scale (DIS) at week-4. Hyoscine and glycopyrronium are clinically effective in treating drooling in children with neurodisability. Hyoscine produced more problematic side effects leading to a greater chance of treatment cessation. These trial results indicate that glycopyrronium should be the drug of first choice. (Parr Jeremy R. et al 2018)

Other Studies

Bachrach et al retrospectively identified and surveyed 54 patients from a cerebral palsy program to inquire about antisialorrheic treatment for excessive drooling. Overall, caregivers reported a decrease in drooling with glycopyrrolate. Glycopyrrolate was used by 37 of 41 respondents, with significant improvement in drooling noted in the vast majority (95%) of cases as indicated by a five-point rating scale [Camp-Bruno (1 - no drooling and 5 - severe drooling)]. A total of 41 questionnaires were completed. The mean reported glycopyrrolate dose was 0.051 mg / kg / dose, usually given 3 times daily; around 86 % of the patients received doses between 0.02 and 0.07 mg / kg / dose. There was a significant difference between the mean baseline scores for all patients and the score after treatment (4.59 vs. 2.41). (Bachrach S. J. et al 1998; Tscheng Dorothy Z. et al 2002; Eiland Lea S. et al 2012 and Reddihough D. S. et al 2011).

A preliminary study was undertaken by Stern L. M. et al to assess the efficacy of an oral anticholinergic drug, glycopyrrolate, in the management of drooling in children and young adults with disabilities. Glycopyrrolate was used by 24 children and young adults for up to 28 months in dose 40 – 100 µg / kg per day with a maximum of 175 µg / kg per day. Parents / care takers were asked to complete a questionnaire on the effects of the drug on severity and frequency of drooling. Of the 22 respondents, there was a statistically significant decrease in both severity and frequency of drooling. Stern concludes that "the majority of subjects show improvement in both severity and frequency of drooling while taking glycopyrrolate." (Tscheng Dorothy Z. et al 2002; Reddihough D. S. et al 2011; Evatt Marian L. et al 2011; Eiland Lea S. et al 2012 and Stern L. M. et al 1997).

Studies involving Adult Patients:

In a 4-week, randomized, double-blind, placebo-controlled, crossover trial, efficacy of glycopyrrolate [1 mg (5 mL) thrice daily] was evaluated in the treatment of sialorrhea in 23 patients with Parkinson disease. Patients were diagnosed with idiopathic parkinson disease according to the UK Parkinson's Disease Society Brain Bank criteria and were required to have marked to severe sialorrhea (a minimum score of 5 on a scale from 1 to 9, tabulated below):

Table 18: Sialorrhea Scoring Scale

Score	Description
1	Dry, never drools
2	Mild, only the lips are wet, occasionally
3	Mild, only the lips are wet, frequently
4	Moderate, wet on the lips and chin, occasionally
5	Moderate, wet on the lips and chin, frequently
6	Severe, drools to the extent that clothing becomes damp, occasionally
7	Severe, drools to the extent that clothing becomes damp, frequently
8	Profuse, clothing, hands, and objects become wet, occasionally
9	Profuse, clothing, hands, and objects become wet, frequently

The patient or caregiver scored the extent of sialorrhea 3 times daily over the daytime period directly preceding the time of drug administration (morning, afternoon, evening) using sialorrhea scoring scale. For every subject, investigators calculated the mean sialorrhea score over the last 3 days of the baseline week, the placebo week, and the glycopyrrolate week separately. The primary outcome measure was the difference in responder rate between glycopyrrolate and placebo whereas the secondary outcome measure was the difference in the mean sialorrhea scores between placebo and glycopyrrolate. Before the onset of the trial, the investigators defined responders as subjects who's mean sialorrhea score improved by at least 30%.

Both primary and secondary outcome measures of sialorrhea improved with glycopyrrolate compared with placebo (refer below table).

Table 19: Efficacy of glycopyrrolate in Parkinson disease

	Glycopyrrolate (n =23)	Placebo (n =23)	*p* value
Primary outcome			
>30% improvement in sialorrhea score	9 (39.1)	1 (4.3)	0.021
Secondary outcome			
Sialorrhea score, mean (SD)	3.8 (1.6)	4.6 (1.7)	0.011

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 sialorrhea score with glycopyrrolate compared with placebo was 0.8 points (bootstrap 95% CI 0.02 – 1.4 points). Nine patients (39.1%) with glycopyrrolate had a clinically relevant improvement of at least 30% vs 1 patient (4.3%) with placebo. The mean improvement in sialorrhea score with glycopyrrolate compared with placebo was 0.8 points. In per protocol analysis, mean sialorrhea score improved from 4.7 with placebo to 3.9 with glycopyrrolate.

In this study, the investigators reported a clinically relevant positive effect of glycopyrrolate on sialorrhea in patients with Parkinson disease. Forty percent of patients experienced an improvement of more than one third on the sialorrhea scoring scale compared with placebo treatment. This finding is in line with positive results of glycopyrrolate on sialorrhea for other indications such as developmentally disabled children and clozapine-induced sialorrhea.

Before the onset of the trial, the investigators had defined responders as subjects who's mean sialorrhea score improved by at least 30%. Although not supported by quality-of-life

measurements, the investigators believed that an improvement of this magnitude should be considered clinically relevant. A 30% improvement on the 9-point sialorrhea scoring scale represents different scores of absolute improvements, depending on the baseline score. The investigators do not consider this to be a problem because they expect a sigmoidal effect curve, i.e., expect that it is more difficult to achieve improvement with lower (better) sialorrhea scores.

This study provides Class I evidence that glycopyrrolate 1 mg 3 times daily is more effective than placebo in reducing sialorrhea in patients with Parkinson disease during a 4-week study.

(Arbouw M. E. L. et al 2010).

Olsen A. K. et al describes the antisialogic effects of oral glycopyrrolate in a patient with tongue cancer suffering from drooling. Treatment was started with an injection of glycopyrrolate 0.2 mg administered subcutaneously which abolished drooling for several hours. The following day, the quantity that had been injected was given orally. A dose of 0.2 mg 3 times daily was tried. After 2 days of treatment, patient was not drooling whereas when the treatment was ceased for 24 hours, the patient reported drooling again. Following treatment for 01-month, patient claimed to have beneficial effect from the glycopyrrolate treatment. (Olsen A. K. et al 1999).

Lucas V. et al reported a case of 84-year-old woman who had undergone numerous operations over a 16-year period for cystic adenocarcinoma of the submandibular salivary gland. Patient was unable to swallow and received enteral feeding via a percutaneous gastrostomy (PEG) tube and presented with main symptom of pooling of saliva which drooled from her mouth. Patient was treated with glycopyrrolate oral suspension 1 mg tds via her PEG tube which improved the drooling to such an extent that she complained of a dry mouth. In summary, enteral glycopyrrolate may be useful in the symptomatic management of drooling. (Lucas V. et al 1998).

Clozapine Induced Sialorrhea (CIS)

Blissit Katie T. et al describe the outcomes of 04 patients who received glycopyrrolate 1 mg tablets for the treatment of CIS. Case 1 and 4 exhibited severe drooling, which caused their clothing, hands and objects to consistently become wet. Case 1 responded well to glycopyrrolate and was restarted on the medication when CIS returned after discontinuation of the drug. Case 2 experienced moderate but frequent drooling. Case 3 displayed a similar response to therapy for CIS as case 1. Glycopyrrolate was effective in alleviating symptoms in three of four patients with CIS. In case 4, the degree of improvement was unknown due to documentation discrepancies; however, mild improvement was noted initially. Results indicate the effective use of glycopyrrolate in patients with CIS. (Blissit Katie T. et al 2014).

Praharaj S. K. et al reported a 35-year-old man with paranoid schizophrenia on clozapine (500 mg/d) therapy, who showed marked reduction in sleep-related sialorrhea following treatment with 1 mg oral glycopyrrolate. On the given clozapine dose, he had persistent sleep-related sialorrhea with associated distress. An estimated area of more than 30-cm diameter of wet surface was spotted regularly over the pillow. There was no daytime sialorrhea. Drugs such as amitriptyline and amisulpride showed minimal reduction in sialorrhea and were discontinued. Glycopyrrolate 1-mg tablet at bedtime was started for sialorrhea, and after few weeks, it reduced to less than 5-cm diameter, with occasional dry days. There was no other emergent adverse event reported with this combination. (Praharaj S. K. et al 2014)

In a randomized, double blind, controlled, crossover, 12-week trial separated by a four-week washout period; efficacy of glycopyrrolate (1 mg twice daily) was compared with Biperiden (2 mg twice daily) for the treatment of Clozapine induced Sialorrhea (CIS) in middle-aged patients with schizophrenia. Initially, 13 patients were treated with either glycopyrrolate or Biperiden. After 4 weeks, both groups had a 4-week washout interval followed by 4 weeks of the alternative treatment. Throughout the trial, the dose of clozapine was maintained. Patients treated with either drug had reduced drooling rating scale scores, Glycopyrrolate treatment gave a significantly greater reduction in patients' DRS scores compared with Biperiden treatment. Patients treated with Biperiden had impaired MMSE scores, which were not present in those treated with glycopyrrolate. Therapeutic response was observed as early as week 1 of treatment and persisted for the duration of glycopyrrolate treatment. Result suggests glycopyrrolate as a valid option for treating CIS. (Liang Chih-Sung et al 2010; Bird Angela M. et al 2011 and Blissit Katie T. et a 20l4).

Effectiveness and tolerability of glycopyrrolate (4 – 8 mg) in treatment of clozapine-induced sialorrhea was evaluated in 03 adolescent female subjects (age 13–16) in an open-label trial. Glycopyrrolate dosing as initiated at 2 mg twice daily in the first two patients and 1 mg three times daily in the third. The dose was titrated based on response, up to maximum of 8 mg/day. The target symptom of sialorrhea was improved in all three cases, with patient self-reports of decreased production of saliva confirmed by staff observation. These three cases provide support for the potential effectiveness of glycopyrrolate for clozapine-induced sialorrhea in adolescents. The authors suggest that glycopyrrolate may be a useful adjunctive therapy for adolescents requiring treatment with clozapine. (Robb A. S. et al 2008 and Buck Marcia L. et al 2010).

Duggal et al reported a case of effective use of glycopyrrolate for clozapine-induced sialorrhea. Subject was noted to have profuse sialorrhea and scored 8 (profuse; clothing, hands, and objects become wet occasionally) on drooling score on a scale used to quantify the severity of sialorrhea. The sialorrhea had started a few weeks after clozapine was initiated, was worse at night and interfered with the patient's social life causing him a lot of embarrassment. Glycopyrrolate was started at 0.5 mg orally b.i.d and was increased to 2 mg b.i.d over 10 days. Within two days of starting glycopyrrolate, subject reported a reduction in sialorrhea, which was dose related, and two weeks after glycopyrrolate was initiated, it had

decreased significantly as demonstrated by a score of 2 (mild; only the lips are wet occasionally) on the scale for assessing the severity of sialorrhea. (Duggal H. S. et al 2007)

In a double-blind randomized crossover trial, 32 patients with nocturnal sialorrhea were enrolled to evaluate the efficacy and safety of glycopyrrolate oral solution (1 mg and 2 mg) in patients using clozapine that experience sialorrhea. The primary outcome was clinical improvement of nocturnal sialorrhea assessed by the Patient Global Impression of Improvement (PGI-I). The proportion of patients with a clinical improvement according to PGI-I between 1 mg and placebo was 18.8% vs. 6.3% and 2 mg and placebo was 43.5% vs. 6.3%. Glycopyrrolate was not associated with severe adverse events or worsening of cognitive adverse events. Compared with placebo, a significantly higher proportion of participants were willing to continue with glycopyrrolate 1 mg once daily and 2 mg once daily. Glycopyrrolate was superior to placebo with 2 mg showing a significant clinical improvement of nocturnal sialorrhea compared with placebo. Glycopyrrolate seemed to be a tolerable anticholinergic agent in the treatment of clozapine-associated sialorrhea. (Man Wai Hong et al 2017)

Efficacy of oral glycopyrronium bromide was determined in comparison with placebo on the severity of complaints of nocturnal sialorrhea in psychiatric patients. Patients received once a day 1 mg glycopyrronium bromide oral solution or an equal volume placebo solution before the night for 6 days, with a washout period after each treatment period. Ten patients participated of which three patients experienced a clinically relevant improvement and 4 patients experienced some improvement on the severity of complaints of CIS after using 2 mg glycopyrronium bromide. The results show that glycopyrronium bromide may potentially be a solution for patients with complaints of CIS. (Koning J. C. A. Colen-de et al 2015)

Risperidone induced Sialorrhea

Hypersalivation has been described commonly with clozapine. Although Risperidone is also seen to be notorious to be causing hypersalivation. Dutta et al reported the use of glycopyrrolate in case of hypersalivation induced by Risperidone who had not responded with conventional anti sialorrhea drugs. A 25 years female patient was treated with Risperidone 3 mg/day and Trihexiphenidyl 2 mg/day for paranoid schizophrenia as per ICD 10 criteria and the dose of Risperidone was tittered to 10 mg/day. Excessive salivation persisted, and she was treated with Clonidine and Biperidin with no outcomes. Later on, she was started tablet Glycopyrrolate 2mg/ day wherein patient showed a dramatic improvement with Tablet and she was maintaining well with tablet Risperidone 10 mg/day, Trihexiphenidyl 8 mg/ day and tablet Glycopyrrolate 2 mg, in her subsequent visit. (Dutta Hemanta et al 2015)

Quality of Life

Control of drooling has reported to show improved quality of life in patients. In a study of 45 children with cerebral palsy, it was reported that control of drooling reduced care needs making daily care less demanding. (Reddihough D. S. et al 2011).

Place in Clinical Practice

Glycopyrrolate or Glycopyrronium bromide is an old drug that has been used for many years orally and via intravenous for its anticholinergic properties and is the first drug treatment approved in the United States for drooling in children with neurologic conditions.

The management of drooling in UK clinical practice was reviewed by Bavikatte et al who discussed the control of sialorrhea (drooling or excessive salivation) in the British Journal of Clinical Practice in 2012. Drooling can result in perioral chapping, irritation, and maceration, with secondary infection of the facial skin, dehydration due to chronic loss of fluids, and increased risk of silent saliva aspiration that can result in recurrent respiratory infections. Anticholinergic medications are been available for many years and have been used to diminish excessive salivation. The authors note that systematic review of anticholinergic drugs show benztropine, glycopyrrolate and benzhexol hydrochloride as being effective in the treatment of drooling but these drugs have adverse side-effects and none of the drugs been identified as superior. Glycopyrrolate studies have shown 70-90% response rates but with 30 - 35% discontinuing due to adverse effects. It is noted that the authors were from the adult Manchester Rehabilitation Unit (Bavikatte et al 2012).

The literature articles proving efficacy of glycopyrrolate in Parkinson disease has been discussed in the relevant efficacy section, however it is just a discussion part as available in the public domain. The applicant doesn't intend to indicate the glycopyrrolate tablet in Parkinson disease.

2.5.5 OVERVIEW OF SAFETY

Glycopyrrolate has been found to be generally well tolerated. While intolerance among individual patients is common due to the well-known effects of anti-cholinergic treatment, serious adverse events are rare and the safety aspects have been documented in a number of trials. The details of undesirable effects of Glycopyrrolate treatment are discussed below.

Kinedexe formulation glycopyrrolate 1 mg and 2 mg tablets are already approved by MHRA for peptic ulcer and is being marketed in the EU region since 2017. Though being approved for peptic ulcer, the general practitioners in EU region are dispensing the tablets for treatment of drooling / sialorrhoea in majority of times. The total number of tablets dispensed / consumed since 19th April 2017 to till date as discussed below:

Product	Quantity dispensed / consumed
Glycopyrrolate 1 mg Tablets	420,120 tablets
Glycopyrrolate 2 mg Tablets	223,230 tablets

The applicant pharmacovigilance system has not reported any severe adverse drug reactions with 1 mg and 2 mg glycopyrrolate tablets during the mentioned duration.

2.5.5.1 Undesirable Effects, Safety and Tolerability

The most common adverse reactions reported with Glycopyrrolate Oral Solution are dry mouth, vomiting, constipation, flushing and nasal congestion. (Cuvposa, Shionogi Inc., 2012 and Drug Watch, 2010; CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

Safety of Glycopyrrolate oral solution appears to be similar to other preparations of Glycopyrrolate. (Cuvposa, Therapeutic Class Review, 2011).

Hypersensitivity reactions to glycopyrrolate may include rash, pruritus, anaphylactic or anaphylactic reactions. Other rare, but serious reactions to glycopyrrolate include arrhythmias, hypotension, hypertension, seizures, and respiratory arrest. (Buck Marcia L. et al 2010).

Glycopyrronium bromide tablets may produce the following effects which are extensions of its fundamental pharmacological actions: dry mouth, difficulty in micturition, inhibition of sweating. Side-effects of antimuscarinics include constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, flushing, and dryness of the skin. Side-effects that occur occasionally include confusion

(particularly in the elderly), nausea, vomiting, and giddiness; very rarely, angle-closure glaucoma may occur. (Glycopyrronium Bromide Tablets, SmPC, 2014)

Interactive Drug Analysis Profile (iDAP) displays an overview of all UK spontaneous suspected Adverse Drug Reactions (ADRs) reported. Below is the collection of adverse events reported with oral administration of glycopyrrolate. (Interactive Drug Analysis Profile for Glycopyrrolate, MHRA, 2018)

Table 20: Adverse Events of Glycopyrrolate from Interactive Drug Analysis Profile

Sr. No.	Adverse Events	All		Fatal AEs
1	Blood and Lymphatic system disorders	0		
2	Cardiac disorders	2		
	Cardiac Flutter		1	
	Atrial Fibrillation		1	
3	Ear and Labyrinth disorders	0		
4	Eye disorders	0		
5	Gastro Intestinal Disorders	6		
	Diarrhoea		1	
	Dysphagia		1	
	Vomiting		1	
	Lip Swelling		2	
	Swollen Tongue		1	
6	General System Disorders	7		
	Pyrexia		2	
	Asthenia		1	
	Chest Discomfort		2	
	Chest pain		1	
	Facial pain		1	
7	Hepatobiliary Disorders	0		
8	Immune System Disorders	2		
	Hypersensitivity		1	
	Reaction to excipient		1	
9	Infections and Infestations	0		
10	Injury, poisoning and procedural complications	0		
10	Investigations	0		
11	Metabolism and Nutritional Disorders	0		
12	Musculoskeletal and Connective Tissue Disorders	2		
	Back pain		1	
	Pain in Extremity		1	
13	Neoplasms Benign, Malignant and Unspecified	0		

Sr. No.	Adverse Events	All		Fatal AEs
14	Nervous System Disorders	4		
	Balance disorder		1	
	Muscle Spasticity		1	
	Febrile Convulsion		1	
	Seizure		1	
15	Psychiatric Disorders	2		
	Social Avoidant Behaviour		1	
	Insomnia		1	
16	Renal and Urinary Disorders	2		
	Dysuria		1	
	Urinary Retention		1	
17	Reproductive System and Breast Disorders	0		
18	Respiratory, Thoracic and Mediastinal Disorders	8		
	Bronchospasm		1	
	Wheezing		1	
	Dyspnoea		2	
	Hyperventilation		1	
	Aspiration		1	1
	Epistaxis		1	
	Pharyngeal Oedema		1	
19	Skin and Subcutaneous Disorders	8		
	Swelling Face		1	
	Urticaria		1	
	Skin Exfoliation		1	
	Rash Erythematous		1	
	Decubitus Ulcer		1	
	Hypohidrosis		1	
	Onychoclasis		1	
	Onychomadesis		1	
20	Social Circumstances	0		
21	Vascular Disorders	0		
	Total	43		1

The applicant has provided safety analysis of patients receiving glycopyrronium from the CPRD database. Around 1083 patients receiving oral glycopyrronium were identified, 579 (53.5%) patients were male and 504 (46.5%) patients were female; 468 patients (43.2%) were children aged ≤17 years: 179 (16.5%) were aged ≤4 years; 289 (26.7%) were aged 5-17 years; 615 patients (56.8%) were adult, aged ≥18 years, with the largest age group (208 patients, 19.2%) being those aged 71 years or older.

In total, 11,824 prescriptions for oral glycopyrronium were issued to the study patients. Mean (SD) duration of prescribing, from first to last prescription, was 561.2 (770.8 days). 887 patients (81.9%) were prescribed oral glycopyrronium as a repeat prescription on at least one occasion; for 664 of these (61.3%), their first oral glycopyrronium prescription was a repeat prescription. 651 patients (60.1%) were prescribed OGP in tablet form only. Of these, 455 patients (42.0%) were prescribed 1 mg tablet only; 126 (11.6%) were prescribed 2 mg tablet only; and 70 (6.5%) were prescribed tablets in both strengths at some time. 331 patients (30.6%) were prescribed oral suspension/liquid only, and 101 patients (9.3%) were prescribed both tablets and oral suspension/liquid in their treatment history.

In this non-comparative, unadjusted analysis of safety events, respiratory events, including respiratory tract infection and cough, were the most commonly recorded over the glycopyrronium prescription period, with constipation the next most frequent. 373 patients had at least one respiratory safety event (respiratory tract infection, pneumonia, or cough) over the follow up period of which the most frequently reported were cough (218 patients), lower respiratory tract infections other than pneumonia (188 patients), and upper respiratory tract infection (172 patients). The serious safety event of pneumonia was recorded in 26 patients. Constipation over the oral glycopyrronium follow-up period was recorded for 110 patients with complications of constipation (including administration of enema, impaction and manual procedures) recorded for four patients. Cardiac safety events of interest were recorded in 20 patients: seven had records of diagnosed hypertension; five of diagnosed hypotension; seven of cardiac rhythm irregularity and two of tachycardia. Urinary retention over the glycopyrronium follow-up period was recorded for four patients.

Glycopyrrolate has been used for several decades in drooling conditions in form of tablets as well as oral solution. The applicant Kinedexe has conducted a bioequivalence study in healthy subjects and the test formulation Glycopyrrolate tablet compared to reference product Cuvposa® oral solution under fasting conditions.

The safety data presented in support of this application has been compiled from published articles; Zeller et al, Stern et al, Arbouw et al, Man et al, Parr et al and Bachrach et al. Most of the adverse events that occurred more frequently in patients treated with glycopyrrolate were typical anticholinergic effects. They included dry mouth/excessive dryness of mouth or secretions, constipation, urinary retention, pneumonia, vomiting, nasal congestion, flushing, behavioural changes, and diarrhoea. Overall, these events occurred quite frequently with frequencies ranging from 10% to 40%. The events are usually mild to moderate in intensity and are dose related i.e. effects are reversible with the reduction in dose or discontinuation of treatment which is in line with current clinical practice followed or recommended.

Stern et al found glycopyrrolate to be well-tolerated in management of drooling in children with disabilities while Arbouw et al concluded that glycopyrrolate 1 mg 3 times daily is a safe therapy for sialorrhea in Parkinson disease. Man et al observed that dosing glycopyrrolate 1

and 2 mg once daily did not result in an increase in adverse events compared with placebo and therefore seems to be a tolerable and safe dose in treating nocturnal sialorrhea.

During the treatment phase, monitoring for side effects is important, and care must be taken to provide appropriate advice to parents, caregivers, and the individuals themselves when prescribing this medication. The dose titration will be 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 physician / prescriber. Moreover, SPC contains detailed instructions on what undesirable effects to look for and how to manage them. The adverse events can be controlled by ensuring adequate titration and monitoring of side effects by the experienced and trained care giver together with physician along with appropriate actions such as stopping / discontinuing the treatment if relevant side effects occur. After evaluation of the adverse effect, a decision should be made about whether glycopyrrolate should be discontinued or restarted at a lower dose.

2.5.5.1.1 Overview of Clinical Safety Data

A preliminary study undertaken by Stern L. M. et al to assess the safety of oral anticholinergic drug, glycopyrrolate, in the management of drooling in children and young adults with disabilities. Glycopyrrolate was used 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. Twenty-two questionnaires were returned. Side-effects included of glycopyrrolate in the management of drooling in children, side-effects report include thirst in hot weather, dilated pupils, flushed face, constipation, bad breath and dry lips. In this preliminary study, glycopyrrolate was found to be well-tolerated in management of drooling in children with disabilities. (Stern L. M. et al 1997).

In placebo-controlled, crossover randomised clinical trial, no serious adverse effects were reported as assessed using a questionnaire at the end of each treatment week in Parkinson's patients receiving Glycopyrronium bromide oral solution or placebo. Dry mouth was the most common adverse effect, experienced by 52.2% patients receiving Glycopyrronium bromide compared with 30.4 % receiving placebo. A change in motor symptoms was reported among 13 % of patients in the Glycopyrronium bromide group versus 17.4% in the placebo group. The following adverse effects were reported equally among the groups: nervousness (21.7%), change in motor symptoms (13%), constipation (13%), vision problems (13%), urine retention (13%), nausea (4.3%) and palpitations (4.3%). The participant that had 5 times the dosage of Glycopyrronium bromide in the first 3 days of treatment experienced marked dryness of the mouth which resolved within a day of stopping the trial. Oral glycopyrrolate 1 mg 3 times daily was a safe therapy for sialorrhea in Parkinson disease. (Glycopyrronium bromide oral solution, Evidence Summary, National Institute for Health Care and Excellence, 2013 and Arbouw M. E. L. et al 2010).

Glycopyrrolate (4 – 8 mg) was generally well tolerated by 03 adolescent female subjects (age 13–16) in an open-label trial in treatment of clozapine-induced sialorrhea. One patient reported constipation, which improved with symptomatic treatment. A second patient reported dry mouth, which improved with a reduction in dose of glycopyrrolate. (Robb A. S. et al 2008).

A double-blind randomized crossover trial evaluated the safety of glycopyrrolate oral solution (1 mg and 2 mg) in 32 patients using clozapine that experience sialorrhea. Glycopyrrolate was not associated with severe adverse events or worsening of cognitive adverse events. Adverse events of glycopyrrolate, in terms of worsening of baseline events, were mild / moderate and included diaphoresis (4.3% - 9.4%), orthostatic hypotension (0% - 9.4%), xerostomia (6.3% - 8.7%), erectile dysfunction (0% -4.8%), shortened sleep (4.3% -6.3%), headache (0% - 6.3%), nervousness (3.1% -4.3%), palpitations (0% -3.1%) and photosensitivity (0% -3.1%). Both dosing glycopyrrolate 1 and 2 mg once daily did not result in an increase in adverse events compared with placebo and therefore seems to be a tolerable and safe dose in treating nocturnal sialorrhea. (Man Wai Hong et al 2017)

Chronic Use of Glycopyrronium:

Below is the discussion on reported uncertainties such as cardiovascular effects, central nervous system effect, developmental effects, urinary retention, pneumonia following the use of glycopyrrolate tablets in patients with long term treatment for chronic pathological drooling.

The safety data presented in support of this application has been compiled from published articles; Zeller et al (2012a and 2012b), Stern et al, Arbouw et al, Man et al, Parr et al and Bachrach et al. Most of the adverse events that occurred more frequently in patients treated with glycopyrrolate were typical anticholinergic effects. They included dry mouth, constipation, urinary retention, pneumonia, vomiting, nasal congestion, flushing, behavioural changes and diarrhoea. Overall, these events occurred quite frequently with frequencies ranging from 10% to 40%.

Products containing the active ingredient have been licensed in Europe for many years including its long-term use in 'special' preparations for the treatment of sialorrhoea. Applicant Kinedexe tablet formulation (1 mg and 2 mg) is also been marketed since 2017 in Europe. The applicant pharmacovigilance database has not revealed any special safety concerns associated with use of glycopyrrolate 1 mg and 2 mg tablets.

The drooling intervention study by Parr et al 2018 compared 02 active drugs (glycopyrrolate and hyoscine) in 90 children (median age 4 years) over a period of 12 weeks and confirmed

the superior safety profile plus an improved tolerability of glycopyrrolate over hyoscine. The trial results indicate that glycopyrrolate should be the drug of first choice in drooling.

Exposure in the open-label study (Zeller et al 2012b) was 24 weeks. Zeller et al assessed the safety and efficacy of glycopyrrolate for 24 weeks in paediatric patients with chronic moderate-to- severe drooling associated with cerebral palsy and other neurologic conditions. Study used a slow dose titration scheme based on the body weight of the child. The clinical data support the safety and tolerability of the drug in indicated population up to 24 weeks.

However, glycopyrrolate 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 and adults with sialorrhoea treated with glycopyrrolate. The purpose of the CPRD study was to assess the paediatric as well as adult patients in the database who had a prescription of glycopyrrolate and diagnosis of drooling.

Cardiovascular Effects:

The cardiovascular effects of glycopyrrolate have been comprehensively investigated (changes in heart rate, blood pressure and cardiac rhythm) in a series of studies in paediatric populations by Rautakorpi P. et al 1998 and Rautakorpi P. et al 1994. The plasma concentration of glycopyrrolate required for effective vagolysis was determined to be at least 10 µg/L. In paediatric studies Rautokorpi (1994 and 1998), plasma concentrations following a 5 µg/kg i.v. dose of glycopyrrolate only briefly exceeded this concentration immediately following administration. Very low plasma concentrations of glycopyrrolate lasting up to 12 hours were reported accompanied by considerable interindividual alterations in kinetic parameters with mean Cmax around 0.37 µg/l.

Significant changes from baseline in heart rate were not seen in any child in either study. In addition, no changes in arterial blood pressure were observed. While in another pharmacokinetic – pharmacodynamic study Cartabuke et al 1991 reported that oral glycopyrrolate (50 µg/kg) has only minor effects on heart rate. 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.

Furthermore, no adverse events related to heart rate and blood pressure are reported in the discussed available clinical studies (Zeller et al, and Parr et al), suggesting no data to support the cardiovascular effects in the target population following glycopyrrolate administration.

Zeller et al 2012(b) performed electrocardiogram assessments and were examined across six dose levels at weeks 4, 12, and 24 by both time averaged and per time point techniques. No abnormal or clinically significant shifts in electrocardiographic findings were observed in

patients with electrocardiographic results at baseline and week 24. The electrocardiographic interval data showed that oral glycopyrrolate had no obvious effect on heart rate or atrioventricular conduction, as measured by PR interval, or depolarization, as measured by QRS duration. There was no evidence of any clinically relevant changes in QTc duration.

There were no reports of adverse events related to cardiovascular effects in the Interactive Drug Analysis Profile MHRA data available in September 2018 (submitted as part of the application) and none have been reported in the post-marketing data of the applicants used tablet. In the CPRD database, cardiac safety events of interest were recorded in 20 patients: seven had records of diagnosed hypertension; five of diagnosed hypotension; seven of cardiac rhythm irregularity and two of tachycardia.

Nevertheless, despite the evidence suggesting minimal or no cardiovascular adverse events due to glycopyrrolate in the target population, the following statement has been added to the SPC: Glycopyrrolate is known to have an effect on heart rate and blood pressure at doses used during anesthesia although clinical trials with chronic drooling have not shown this effect. An effect on the cardiovascular system should be considered when assuming tolerability.

Central Nervous System Effects:

Glycopyrrolate is reported to be preferable to the other anticholinergic drugs because of its long duration of action and inability to cross the blood–brain barrier, thus minimizing central nervous system adverse effects. As glycopyrrolate possesses a highly polar quaternary ammonium group, its passage across lipid membranes (e.g. the blood-brain barrier) is limited. A study involving patients aged 1 month to 9 years with hydrocephalus reported that intravenous atropine appeared to have greater penetration of the blood brain barrier than intravenous glycopyrrolate. (Garnock-Jones Karly P. et al 2012, CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

In the studies by Zeller et al 2012a and Zeller et al, 2012b, no central nervous system related effects were reported.

The low affinity for glycopyrrolate to cross the blood brain barrier, compared to other anticholinergic drug is clearly seen in the drooling intervention study by Parr et al 2018. The author compared glycopyrrolate and hyoscine in a 12-week trial in children, non-predicted side effects leading to withdrawal showed hyoscine to be associated with; ataxia (3), hyperactivity (2), floppiness (1) and increased seizure activity (1); while glycopyrronium was associated with 1 episode of hyperactivity.

Only 02 reports of adverse events related to psychiatric disorders in the Interactive Drug Analysis Profile MHRA data available in September 2018 (submitted as part of the

application) and none have been reported in the post-marketing data of the applicants used tablet.

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 glycopyrrolate and in those with compromised blood brain barrier. The specific behavioural changes mentioned in the published studies have been included as possible adverse events in SPC, which also includes the following warning in SPC: 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 patients with compromised blood brain barrier.

Neurodevelopment Effects

Based upon the data in the public domain, no reports in the scientific literature of adverse effects of glycopyrrolate on neurodevelopment were identified. By 3 years of age healthy children would be expected to have a sufficiently well-developed blood brain barrier and glycopyrrolate, when given in the doses proposed by the applicant, would not be expected to result in neurodevelopmental effects. There were no reports of adverse events related to neurodevelopment, including growth (weight and height), in the Interactive Drug Analysis Profile MHRA data available in September 2018 (submitted as part of the application) and none have been reported in the post-marketing data of the applicants used tablet. Given that glycopyrrolate 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 test formulation.

Urinary Retention

Urinary retention is a known complication of anticholinergic treatment, with 3 cases (15%) occurring in the placebo-controlled study (Zeller, 2012a). Bachrach et al reported 19% patients with urinary retention with glycopyrrolate treatment.

Only 01 report of adverse event urinary retention is reported in the Interactive Drug Analysis Profile MHRA data available in September 2018 (submitted as part of the application) and none have been reported in the post-marketing data of the applicants used tablet. Urinary retention over the glycopyrronium follow-up period was recorded for four patients in the CPRD database.

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 SPC advises that urinary retention is a known adverse reaction associated with

anticholinergic medicinal products (5.4%). Glycopyrronium treatment should be withdrawn until the urinary retention resolves.

Pneumonia

Pneumonia is a known complication associated with glycopyrrolate treatment. Pneumonia was reported 7.9% patients in the Zeller et al 2012(b)-study following the treatment with glycopyrrolate. No other data is available from public literature references with regards to reporting pneumonia following glycopyrrolate treatment.

There were no reports of pneumonia in the Interactive Drug Analysis Profile MHRA data available in September 2018 (submitted as part of the application) and none have been reported in the post-marketing data of the applicants used tablet.

Data from the applicant CPRD collection shows that respiratory safety events were the most frequently observed, with a rate of 244.2 pkpy (per thousand per year), these included common respiratory infections and cough and this figure may therefore not be remarkable. For the more serious safety event of pneumonia (recorded in 26 patients), the rate was 17.0 pkpy (per thousand per year), but it is unknown what role age and treatment indication may have to play here.

The applicant SPC advises that pneumonia is a known adverse reaction associated with anticholinergic medicinal products (7.9%). Glycopyrronium treatment should be withdrawn until the pneumonia resolves if it occurs which is the current followed practice in clinical settings.

Summary of the discussed safety uncertainties:

The following summarizes the data provided to justify the position that safety data has been sufficiently characterized in terms of chronic use, cardiovascular effect, central nervous system effects, developmental effects, urinary retention and pneumonia.

- From the available data there appears to be an inverse association between continued use of glycopyrrolate and incidence of adverse events.

- Adverse events can be effectively managed through optimizing dose to balance efficacy with tolerability.

- Adverse events only lead to treatment withdrawal in a small percentage of subjects (Parr et al).

- The significant adverse events of urinary retention, constipation and pneumonia are associated with use of glycopyrronium, as evidenced by clinical trials and CPRD data. These events have the potential for significant clinical implications and evidence from CPRD suggests treatment discontinuation.

- The applicant has included urinary retention, constipation and pneumonia in the SPC as adverse events requiring treatment discontinuation should they occur.

- There is no information in the published literature to suggest an effect of glycopyrrolate on neurodevelopment or growth (height and weight).

- The SPC 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 that no new or unexpected events are evident despite long-term treatment with glycopyrrolate in many patients. The adverse events known to occur can be effectively managed through dose titration or treatment withdrawal in line with current clinical practice. 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.

Based on the available data, it is evident that the safety of glycopyrrolate in the applicant's product for the proposed indication has been adequately characterized in particular for chronic use, cardiovascular effect, central nervous system effects, developmental effects, urinary retention and pneumonia. 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 glycopyrrolate in the target population and justifies a positive opinion on the licence application.

2.5.5.1.2 Safety for Pregnancy and Lactation

Pregnancy:

There are no available data in pregnant women for glycopyrrolate to inform decisions concerning any drug-associated risks. In pregnant rats, daily oral administration of glycopyrrolate during organogenesis at dose exposures 2.5 to 113 times the exposure at the maximum recommended human dose (MRHD) did not result in an increased incidence of gross external or visceral defects. When glycopyrrolate was administered intravenously to pregnant rabbits during organogenesis at dose exposures equivalent to up to approximately

7.8 times the exposure at the MRHD, no adverse effects on embryo-fetal development were seen. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

Glycopyrrolate does not penetrate the blood-brain or placental barrier in significant amounts and consequently seldom causes central nervous system or neonatal toxicity. (Kanto J. et al 1988)

Glycopyrrolate 0.005 mg/kg intravenously administered to normal full-term parturient in labour does not cross the placenta to any significant degree to affect fetal heart rate and fetal heart rate variability. Uterine activity increased in a normal manner as labour progressed. (Abboud Therese et al 1983)

The effects of i.v. glycopyrrolate on maternal and foetal heart rate, heart rate variability, and maternal electromechanical intervals and blood pressure were evaluated in 20 term parturient in labour. There were no significant changes in foetal heart rate or foetal heart rate variability. The maternal heart rate increased in all cases and the electromechanical interval decreased with the onset of maternal tachycardia. There were no significant changes in maternal blood pressure. Uterine activity increased in all cases; however, this increase does not appear to be greater than that expected as labour progresses. (Abboud T. K. et al 1981)

The safety of this drug during pregnancy has not been established. The use of drug during pregnancy requires that the potential benefits of the drug be weighed against possible hazards to mother and child. [CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals]

Lactation:

There are no data on the presence of glycopyrrolate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for glycopyrrolate and any potential adverse effects on the breastfed infant from glycopyrrolate or from the underlying maternal condition. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

2.5.5.1.3 Safety in Children

Glycopyrrolate oral solution was evaluated for chronic severe drooling in patients aged 3 to 16 years with neurologic conditions associated with problem drooling. Safety of drug has not been studied in subjects under the age of 3 years. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Cuvposa, Therapeutic Class Review, 2011).

In pediatric clinical trials conducted with Glycopyrrolate oral solution, the most common adverse reactions included dry mouth (40%), vomiting (40%), constipation (35%), flushing (30%), nasal congestion (30%), headache (15%), sinusitis (15%), upper respiratory tract infection (15%) and urinary retention (15%). (Buck Marcia L. et al 2010).

Glycopyrrolate oral solution was well tolerated in children with problem drooling associated with neurologic conditions. In a placebo-controlled randomised trial, all 20 patients aged 3 – 23 years 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. During the first 4 weeks, Glycopyrrolate 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. After the optimal dose level was reached, patients continued to receive the same medication and dose, for a total of 8 weeks.

Four patients (20 %) in the glycopyrrolate oral solution group, but none in the placebo group, had at least one severe TEAE. One patient (5.0 %) in the glycopyrrolate oral solution 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. One patient in the glycopyrrolate oral solution group (5.0%) and one in the placebo group (5.6%) discontinued treatment because of a TEAE. The most common adverse effects occurring in the glycopyrronium bromide group were: dry mouth (8 of 20; 40%), constipation (6 of 20; 30%), vomiting (6 of 20; 30%), nasal congestion (6 of 20; 30%), flushing (5 of 20; 25%) and urinary retention (3 of 20; 15%). The most common adverse effects occurring in the placebo group were constipation (4 of 18; 22%) and flushing (3 of 18; 17%). Of all AEs reported in the study, 39.9% were identified by the parent / caregiver, and 4.5% by the investigator. Glycopyrrolate oral solution was found to be generally well tolerated in all the patients including children aged between 3 – 16 years of age.

Table 21: Treatment-emergent Adverse Reactions occurring in ≥ 15 % of Patients treated with Glycopyrrolate Oral Solution (1 mg / 5 mL) and 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

[Garnock-Jones Karly P. et al 2012; Zeller Robert S. et al 2012(a); Glycopyrronium bromide oral solution, Evidence Summary, National Institute for Health Care and Excellence, 2013 and Cuvposa, Shionogi Inc., 2012].

In 137 intent-to-treat paediatric patients in a multicenter, open-label 24-week trial evaluating the safety of CUVPOSA® (containing Glycopyrrolate oral solution), most of the patients (89 %) reported at one treatment-emergent adverse events, 47 % of which were deemed related to CUVPOSA® with most being mild to moderate in intensity. To provide more accurate pediatric dosing and titration, glycopyrrolate was started at a dose of 0.02 mg/kg three times daily, with dose increases to 0.04, 0.06, 0.08, and 0.10 mg/kg. The most commonly reported (more than 5%) treatment-emergent adverse events were constipation (20.4%), vomiting (17.5%), diarrhea (17.5%), pyrexia (14.6%), dry mouth (10.9%), flushing (10.9%) and nasal congestion (10.9%). Nineteen patients (13.9%) discontinued treatment due to an adverse event, but no adverse event was specifically associated with discontinuation. Fourteen patients reported 20 serious adverse events, 04 were considered treatment-related such as nystagmus, esophageal candidiasis, dehydration and gastrointestinal motility disorder. Of these 14 patients with serious adverse events, 08 were while taking the study drug and six within 30 days of the last dose. The mean daily dose of oral glycopyrrolate solution was 0.15 mg/kg, with 70 of the 137 patients (51.1%) receiving a mean daily dose of ≥0.1 mg/kg to ≤0.2 mg/kg, and 10 (7.3%) receiving the maximum dose of 0.1mg three times daily.

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 0.0%), 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 0.0%), pyrexia (18.4% versus 15.7% versus 6.9%) and rash (5.3% versus 11.4% versus 3.4%). Clinically significant toxicity grade shifts, from grade 0 at baseline to grade 2 at week 24/exit visit, were observed in two patients, one in platelet count (from 3.9×10^5 / µL at baseline to 6.7×10^4 / µL at week 24 / exit visit) and one in calcium concentration (from 9.2 mg / dL at baseline to 7.2 mg / dL at week 24 / exit visit). Oral Glycopyrrolate solution 1 mg / 5 mL for chronic moderate-to-severe drooling associated with cerebral palsy or other neurologic conditions was well tolerated over 24 weeks by pediatric patients aged 3 – 18 years.

[Garnock-Jones Karly P. et al 2012; Zeller Robert S. et al 2012(b) and Cuvposa, Shionogi Inc., 2012].

Bachrach et al retrospectively identified and surveyed 54 paediatric patients with cerebral palsy in antisialorrheic treatment for excessive drooling. Glycopyrrolate was used by 37 of 41 respondents. For the 37 patients receiving glycopyrrolate, the mean dose was 0.051 mg/kg/dose, with a range of 0.01 to 0.14 mg/kg/dose, most commonly given three times a

day. Almost 46% of the patients experienced an adverse drug reaction. The most common complaints were dry mouth and / or thick secretions (19%), urinary retention (19%), flushing (11%), and constipation (5%). Of the three patients who were receiving more than 0.1 mg/kg/dose, two experienced no side effects. Eleven (30%) of the 37 patients had discontinued the medication anywhere from 1 to 20 months after starting medication. Of these 11 patients, one discontinued the medication because of ineffectiveness. The other 10 stopped because of unwanted side effects. The dose of glycopyrrolate in those who discontinued the medication was 0.053 mg/kg/dose compared with 0.051 mg/kg/dose in those who continued with the medication at the time of follow-up. (Bachrach S. J. et al 1998; Eiland Lea S. et al 2012 and Tscheng Dorothy Z. et al 2002).

In a pediatric trial in patients with hyperhidrosis, side effects were noted in 29% of the intent-to-treat patients following oral administration of Glycopyrrolate tablets and were largely confined to dry mouth / increased thirst (26 %) and dry eyes (10 %). The dryness was dose-related and improved when the dosage was lowered (i.e. present at 3 mg daily but not at 1 mg daily), allowing partial amelioration of the hyperhidrosis while minimizing drying side effects. One patient reported tachycardia following 1 mg twice daily dosing while another one patient experience blurred vision with a dosage of 5 mg daily (in two divided doses). Overall, 18% of pediatric patients who found improvement experienced an adverse effect at a dose of less than or equal to 2 mg daily. (Paller Amy S. et al 2012).

In a retrospective analysis of oral glycopyrrolate used for hyperhidrosis at a single pediatric center in 12 pediatric patients, 07 patients reported side effects such as dry mouth (n = 6), constipation (n = 1), dizziness (n = 1) and facial swelling (n = 1). Glycopyrrolate was reported to be well tolerated in paediatric patients with hyperhidrosis. (Kumar M. G. et al 2014).

Safety of hyoscine patch and glycopyrronium liquid was studied in treatment of drooling in children with neurodisability. Predictable side effects were reported less frequently by parents of children who received hyoscine 22/47 (46.8%) than glycopyrronium 24/38 (63.2%). Those most commonly reported for hyoscine and glycopyrronium respectively were: unwell 14/47 (29.8%) vs 15/38 (39.5%); constipation 5/47 (10.6%) vs 12/38 (31.6%); excessive drying of respiratory/oral secretions 3/47 (6.4%) vs 7/38 (18.4%); skin flushing/dryness 8/47 (17.0%) vs 3/38 (7.9%). Other side effects were seen in less than two children per treatment arm. Hyoscine was associated with more problematic predictable side effects leading to children stopping medication than glycopyrronium. Seventeen parents from the hyoscine arm reported a predictable side effect that led to cessation of their child's medication [11 with skin reactions to patches (redness, blistering, swelling, skin breakdown), one with dry mouth, one with pupil dilation and four repeatedly pulled off their patches]. This compares to only six parents reporting a predictable side effect leading to cessation of glycopyrronium (two with dry mouth, two with constipation and two with skin dryness or rash). Children receiving hyoscine also stopped medication due to non-predictable side-effects more frequently than those receiving glycopyrronium. Seven children on hyoscine stopped medication (three with

unsteady walking, two with hyperactivity, one with floppiness, one with increased seizure activity). One child on glycopyrronium stopped medication due to hyperactivity. (Parr Jeremy R. et al 2018)

No efficacy and safety data are been available in the public domain in patients below the age of 3 years and hence acceptable safety for these patients can't be established for glycopyrrolate Hence, the applicants licensed indication is restricted to patients aged 3 years and older. The applicants tablet product is unsuitable for younger children (under approximately 31 kg) and hence for such kind of patient population other pharmaceutical forms should be used.

2.5.5.1.4 Safety in Patients with Renal Impairment

Since glycopyrrolate is largely renally eliminated, the drug should be used with caution in patients with renal impairment. (CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Garnock-Jones Karly P. et al 2012).

The pharmacokinetics of glycopyrronium bromide reflect that it is largely eliminated unchanged by the kidneys. Approximately 65%-80% of an intravenous glycopyrrolate dose was eliminated unchanged in urine in adults. (Buck Marcia L. et al 2010).

In one study glycopyrrolate was administered IV in uremic patients undergoing renal transplantation. The mean elimination half-life was significantly longer (46.8 minutes) than in healthy patients (18.6 minutes). The mean area-under-the-concentration-time curve (10.6 hr-µg/L), mean plasma clearance (0.43 L/hr/kg), and mean 3-hour urine excretion (0.7%) for glycopyrrolate were also significantly different than those of controls (3.73 hr-µg/L, 1.14 L/hr/kg, and 50%, respectively). These results suggest that the elimination of glycopyrrolate is severely impaired in patients with renal failure. (Buck Marcia L. et al 2010, CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018)

Therefore, any degree of renal impairment is likely to have a significant effect on its elimination and therefore a dose adjustment would be needed to ensure safe use. It is recommended that the drug is not used in patients who have severe renal impairment and use with caution in patients who have mild to moderate renal impairment.

2.5.5.1.5 Safety in Elderly

Use glycopyrrolate with caution in the elderly and in all patients with:

- Autonomic neuropathy.
- Renal disease.

- Ulcerative colitis–large doses may suppress intestinal motility to the point of producing a paralytic ileus and for this reason may precipitate or aggravate "toxic megacolon," a serious complication of the disease.
- Hyperthyroidism,
- Coronary heart disease, congestive heart failure, cardiac tachyarrhythmias, tachycardia, hypertension and prostatic hypertrophy.
- Hiatal hernia associated with reflux esophagitis, since anticholinergic drugs may aggravate this condition.

[CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018]

There is limited data available on the specific adverse effects of glycopyrronium bromide in the elderly and therefore this population is advised against using glycopyrronium bromide. According to the Beers Criteria 2019, systemic anticholinergic medications should be avoided in geriatric patients with the following due to the potential for symptom exacerbation or adverse effects: dementia/cognitive impairment (adverse CNS effects), delirium/high risk of delirium (possible new-onset or worsening delirium), or lower urinary tract symptoms/benign prostatic hyperplasia in men (possible urinary retention or hesitancy). (Samuel M. J. et al 2019)

Because of its quaternary structure, glycopyrronium bromide is known not to penetrate the blood brain barrier and in theory therefore has a lesser potential for CNS effects. However, caution is applied and this population is contraindicated to use glycopyrronium bromide. [CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018]

In a study done by Ali-Melkkila et al, PK-PD correlation of glycopyrronium, a and reproducible radio receptor assay (RRA) was used to study the pk /pd sensitive comparison between intramuscular and oral use of glycopyrronium. After oral drug intake, 4 mg (n = 6), an apparently low and variable gastrointestinal absorption was found (Tmax = 300.0 ± 197.2 min, Cmax = 0.76 ± 0.35 µg/1), thus indicating that the oral route of drug administration is of no value as a routine premedication. The correlation between the plasma concentration of glycopyrrolate and the drug effects appears to be variable. (Ali-Melkkila et al 1989). This variable GI absorption is likely to be more pronounced in elderly and therefore the use of glycopyrronium for this population remains contraindicated.

2.5.5.2 Overdosage

Signs and Symptoms:

Since Glycopyrrolate is a quaternary amine which does not easily cross the blood-brain barrier, symptoms of glycopyrrolate overdosage are generally more peripheral in nature rather than central compared to other anticholinergic agents. [CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018].

Following an overdose, penetration of glycopyrrolate into the central nervous system may result in agitation, restlessness, or psychotic behavior. (Buck Marcia L. et al 2010).

Treatment:

In case of accidental overdose, therapy includes:

- Maintaining an open airway, providing ventilation as necessary.
- Managing any acute conditions such as hyperthermia, coma and or seizures as applicable and managing any jerky myoclonic movements or choreoathetosis which may lead to rhabdomyolysis in some cases of anticholinergic overdosage.
- Administering a quaternary ammonium anticholinesterase such as neostigmine to help alleviate peripheral anticholinergic effects such as anticholinergic induced ileus.
- Administering activated charcoal orally as appropriate.

(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018).

2.5.5.3 Contraindications

Glycopyrrolate is contraindicated in:

- Patients with medical conditions that preclude anticholinergic therapy (e.g., glaucoma, paralytic ileus, gastrointestinal obstruction, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis).
- Patients taking solid oral dosage forms of potassium chloride. The passage of potassium chloride tablets through the gastrointestinal (GI) tract may be arrested or delayed with coadministration of Glycopyrrolate.

[CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018; Cuvposa, Shionogi Inc., 2012; Buck Marcia L. et al 2010; Wadhawan R. et al 2014; Zeller Robert S. et al 2012(a)].

2.5.5.4 Warnings and Precautions

Constipation or Intestinal Pseudo-obstruction -

Constipation is a common dose-limiting adverse reaction which sometimes leads to glycopyrrolate discontinuation. Assess patients for constipation, particularly within 4 - 5 days of initial dosing or after a dose increase. Intestinal pseudo-obstruction has been reported and may present as abdominal distention, pain, nausea or vomiting.

Incomplete Mechanical Intestinal Obstruction -

Diarrhea may be an early symptom of incomplete mechanical intestinal obstruction, especially in patients with ileostomy or colostomy. If incomplete mechanical intestinal obstruction is suspected, discontinue Glycopyrrolate treatment and evaluate for intestinal obstruction.

High Ambient Temperatures -

In the presence of high ambient temperature, heat prostration (fever and heat stroke due to decreased sweating) can occur with use of anticholinergic drugs such as Glycopyrrolate. In such case parents / caregivers should be advised to avoid exposure of the patient to hot or very warm environmental temperatures.

Anticholinergic Drug Effects -

Use Glycopyrrolate with caution in patients with conditions that are exacerbated by anticholinergic drug effects including:

- Autonomic neuropathy
- Renal disease
- Ulcerative colitis – Large doses may suppress intestinal motility to the point of producing a paralytic ileus and for this reason may precipitate or aggravate "toxic megacolon," a serious complication of the disease.
- Hyperthyroidism
- Coronary heart disease, congestive heart failure, cardiac tachyarrhythmias, tachycardia, and hypertension
- Hiatal hernia associated with reflux esophagitis, since anticholinergic drugs may aggravate this condition

(CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Cuvposa, Shionogi Inc., 2012; Cuvposa, Shionogi Inc., 2012]

2.5.5.5 Effects on Ability to Drive and Use Machines

Glycopyrrolate may produce drowsiness or blurred vision. Hence patients should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. [CUVPOSA Oral Solution, FDA Label of Merz Pharmaceuticals, 2018 and Cuvposa, Shionogi Inc., 2012]

2.5.5.6 World-wide Experience

Glycopyrrolate was approved for use by the Food and Drug Administration (FDA) in 1961 in the preoperative setting or during procedural sedation to reduce salivary, pharyngeal and bronchial secretions, reduce the volume and acidity of gastric secretions, and block cardiac vagal inhibitory reflexes during induction and intubation. On July 29, 2010; Glycopyrrolate oral solution was approved by the FDA for the treatment of chronic severe sialorrhea caused by neurologic conditions in pediatric patients between 3 and 16 years of age. (Glycopyrrolate Oral Solution, Drug Bulletin, 2011 and Buck Marcia L. et al 2010).

2.5.5.7 Newer or Different Issues Identified

No newer or different safety issues of the Glycopyrrolate Oral Solution have so far been identified.

2.5.6 BENEFITS AND RISKS CONCLUSIONS

The application for Glycopyrrolate tablets 1 mg and 2 mg is made according to Article 10(a) of Directive 2001/83/EC as amended. The clinical pharmacological characteristics of Glycopyrrolate 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 study 934-19 comparing the to-be-marketed Glycopyrrolate 2 mg tablets of Kinedexe Limited, U.K. with the reference product Cuvposa® oral solution 1 mg/5mL of Glycopyrrolate as 1 mg/5mL of Glycopyrronium Bromide (dose of 10 mL equivalent to 2 mg of Glycopyrronium Bromide) manufactured for Merz Pharmaceuticals, LLC.

The products proposed indication is for the symptomatic treatment treatment of severe sialorrhoea (chronic pathological drooling) due to chronic neurological disorders of childhood onset in patients 3 years and older.

The tablet product is unsuitable for younger children (under approximately 31 kg), for this patient population other pharmaceutical forms should be used.

No efficacy and safety data are been available in the public domain in patients below the age of 3 years and hence acceptable safety for these patients can't be established for glycopyrrolate Hence, the applicants licensed indication is restricted to patients aged 3 years and older.

As described by Bavikatte et al (Bavikatte et al 2012) glycopyrrolate is one of three anti-cholinergic treatments that have been found to be effective in the treatment of drooling and none of the drugs has been identified as superior. Clinical studies have shown 70-90% response rates but with 30 -35% discontinuing due to adverse effects. The authors include glycopyrronium as a treatment option in their clinical practice review and it is noted that the authors were physicians in adult medicine affiliated to the Manchester Rehabilitation Unit (Bavikatte et al 2012). While the majority of the evidence for clinical efficacy and safety discussed above derives from studies in children it is accepted as applying to adult patients as confirmed by clinical studies, including that of Arbouw (Arbouw 2010) which provides Class I evidence that glycopyrrolate 1 mg 3 times daily is more effective than placebo in reducing sialorrhea during a 4-week study, and as found in clinical practice.

The data presented in this application confirm that glycopyrrolate has been used regularly in clinical practice for this specific, uncommon, indication, that is for the treatment of severe chronic pathological drooling in adults with chronic neurological disorders, relieve for many years before after the clinical effects in peptic ulcer became redundant. The interest in the product has been necessarily limited to specialised units but the findings in adults and children are coherent. The clinical benefits have been confirmed in numerous studies and the adverse reactions have been those associated with anti-cholinergic medicines. Serious adverse reactions are rare and the common adverse reactions seldom severe and probably better

tolerated in adults than in children. The similarity of the applicant's formulation has been shown to correspond to that of products reported in the literature. On this basis the requirements for acceptance of this 10(a).

The use of glycopyrrolate in adults is for the treatment of severe drooling associated with advanced neurological disease. The patients are often near the end of life so that the clinical need for the alleviation of symptoms is great. There has been no perceived need for large scale clinical studies so that the data base is relatively sparse. However, it is apparent that the application is for use in an important area of clinical need.

Because of its quaternary structure, glycopyrronium does not cross the blood–brain barrier, a characteristic that theoretically makes it more tolerable in patients with central nervous system impairments. It may be considered a preferred option among anticholinergic drugs because of its long duration of action and inability to cross the blood–brain barrier, thus minimizing central nervous system adverse effects such as sedation, dysphoria, and restlessness.

The desired antisecretory effects of anticholinergics are accompanied by predictable side effects, such as dry mouth and constipation. Important potential adverse events specified in the prescribing information of Glycopyrrolate include dry mouth, constipation, vomiting, nasal congestion, flushing, behavioural changes, urinary retention and diarrhoea. These events occurred with frequencies ranging from 10% to 40% and seem to be dose dependent.

Based on above it is concluded that glycopyrrolate oral solution and tablets are considered to have a positive benefit risk in the indication for the amelioration of severe drooling in adults.

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