CENTER FOR DRUG EVALUATION AND RESEARCH

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	06/15/2010
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Subject:	Expected Mortality Rate in Children and Adolescents with Cerebral Palsy
Drug Name(s):	Glycopyrrolate
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EXECUTIVE SUMMARY

The Division of Epidemiology (DEPI) surveyed peer-reviewed pediatric cerebral palsy mortality rates in order to better understand whether the mortality rate observed in the Sc-GLYCO-06-01 open-label trial of glycopyrrolate for the treatment of pathologic drooling in pediatric patients with cerebral palsy and other neurologic diagnoses was greater than would be expected in this population.

DEPI does not recommend that comparisons to published cerebral palsy mortality rates be used to determine if the three deaths observed in the Sc-GLYCO-06-01 trial were due to glycopyrrolate or were just the expected number of deaths given the background mortality rate in this population.

Qualitative comparisons between the mortality rate observed in the Sc-GLYCO-06-01 trial and those published from unselected cohorts of pediatric cerebral palsy patients older than one year of age did not provide sufficient evidence to unequivocally conclude that the Sc-GLYCO-06-01 mortality rate was different than the expected background rate. The mortality rate in Sc-GLYCO-06-01 trial was 45.6/1000 person-years (95% confidence interval: 14.7-141.4); higher than point estimates from unselected pediatric cerebral palsy cohorts. However, the lower bound of the 95% confidence interval for the Sc-GLYCO-06-01 trial encompassed the mortality rates reported for more severely disabled cerebral palsy patients from the aforementioned cohort studies. More severe disability, indicated by use of feeding tubes, profound intellectual impairment, or quadriplegia, was associated with an increased risk of death in the pediatric cerebral palsy cohort studies. The Sc-GLYCO-06-01 trial had greater proportion of severely disabled patients than did the pediatric cerebral palsy cohorts. For example, 51.1% of patients in the Sc-GLYCO-06-01 trial required a feeding tube, whereas only 6.0%-7.6% of cerebral palsy patients in the cohort studies needed a feeding tube. Therefore, it is possible that the marked differences in the prevalence of quadriplegia, intellectual impairment, and use of feeding tubes explained the discrepancy between the mortality rate observed in the Sc-GLYCO-06-01 trial and the mortality rates published from these cohort studies. However, this hypothesis was not tested with formal statistical tests that could adjust for the differences in patient characteristics due to Sc-GLYCO-06-01's small sample size, and the lack of source data from the cohort studies.

Other data from the clinical development program or the post-marketing period may better address this question.

1 INTRODUCTION

The Division of Dermatology and Dental Products (DDDP) requested the Division of Epidemiology (DEPI) to estimate the background mortality rate in patients 3 to 18 years of age with cerebral palsy and other disabling neurologic conditions. The overarching purpose of this consult was to determine if the number of deaths observed in a phase-III single arm trial of glycopyrrolate was greater than would be expected in a population of pediatric patients with cerebral palsy and other disabling neurologic conditions.

Glycopyrrolate (glycopyrronium bromide) is an anticholinergic originally approved for the adjunctive treatment of peptic ulcers in adults, and as a preoperative or intraoperative medication for the inhibition of salivation and excessive secretions of the respiratory tract in adults and children 2 years of age and older. Oral glycopyrrolate has been used off-label for the management of drooling associated with neurodevelopmental disorders.

The Sponsor has submitted an NDA for the use of oral liquid glycopyrrolate for the treatment of (b) (4) (chronic (b) (4) severe) drooling in patients 3 to (b) (4) years of age with cerebral palsy or other neurologic conditions. Two phase-III clinical trials were submitted in support of this NDA; an eight week, randomized, double-blind, placebo-controlled trial with 38 subjects and

a twenty-four week, open-label, single-arm trial with 137 subjects. Patients in the two trials were similar on most clinical factors except for feeding tube use; more patients in the open-label trial required a feeding tube compared to the patients in the placebo-controlled trial (32% versus 51.1%).

Three deaths occurred during the open label trial (protocol Sc-GLYCO-06-01), but no deaths occurred during the double-blind, placebo-controlled trial (protocol FH-00-01). All three deaths occurred within the thirty-day period post last study drug administration. The DDDP dental officer reviewing this NDA has communicated that the causes of death were not conclusively related to known anticholinergic side-effects associated with glycopyrrolate. Without comparison data from a placebo arm, data from the Sc-GLYCO-06-01 trial was insufficient to determine whether or not these three deaths were due to glycopyrrolate or were just the expected number of deaths given the background mortality rate in this population.

2 METHODS AND MATERIAL REVIEWED

2.1 METHODS

To assess whether deaths occurred more frequently than expected in the Sc-GLYCO-06-01 trial, a mortality rate was calculated from the trial data and a literature search was conducted to find a background mortality rate in a comparable population.

The trial's mortality rate was expressed in terms of a person-year rate; calculated by dividing the number of deaths by the total person-time observed in the intent to treat (ITT) population. An exact 95% Poisson confidence interval (CI) was calculated for this estimate.

Mortality was expressed in terms of person-years rather than a survival curve or an actuarial table in order to account for the trial's short duration and variable follow-up between patients, in addition to the clustering of events in the thirty day period post last study drug administration. The person-year method also allowed for the calculation of a single point estimate and a confidence interval which facilitated qualitative comparisons to previously published mortality rates.

The literature review was restricted to cerebral palsy studies due to the difficulty in finding a sample with a comparable distribution of neurologic diagnoses and associated disability. Although imperfect, a restricted literature review was believed to be somewhat relevant to the ITT population in the Sc-GLYCO-06-01 trial. Even though patients with a variety of disabling neurologic conditions, such as seizure disorders and DiGeorge syndrome, were eligible for this trial, the ITT population was mostly cerebral palsy patients (70.1%). In addition, all three deaths occurred in cerebral palsy patients.

Background cerebral palsy mortality rates were obtained from the peer-reviewed literature by conducting a search in PubMed/MEDLINE for English-language articles related to mortality or life-expectancy in cerebral palsy patients on May 5, 2010. The following PubMed/MEDLINE query was used: {"cerebral palsy"[All Fields] AND English [lang] AND (("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) OR ("death"[MeSH Terms] OR "death"[All Fields]) OR "life expectancy"[All Fields]).

Any peer-reviewed article identified by the literature search was included in this review if it provided a mortality rate in terms of person-years for pediatric cerebral palsy patients older than one year of age. Studies which reported on selected samples, such as cerebral palsy in premature births or postnatal cerebral palsy, were excluded.

Due to limitations that are discussed in a later section, formal statistical tests were not conducted to test the hypothesis that the mortality rate observed in the Sc-GLYCO-06-01 trial was different

than the expected mortality rate in pediatric cerebral palsy. As such, the discussion will be based on a qualitative comparison of the point estimates and 95% confidence intervals. To facilitate these qualitative comparisons, mortality rates stratified by gender were collapsed and rates stratified by age were recalculated to better match the age range in Sc-GLYCO-06-01. Also, exact 95% Poisson CIs (95% CI) were calculated for each mortality rate selected from the peer-reviewed literature. This was possible since all selected studies provided the number of deaths and total person-years for each stratified mortality rate.

2.2 MATERIALS REVIEWED

The following materials were reviewed in this consult:

- Sc-GLYCO-06-01 trial data (provided by Sponsor)
- Blair, E., Watson, L., Badawi, N., & Stanley, F. J. (2001). Life expectancy among people with cerebral palsy in Western Australia. *Developmental medicine and child neurology, 43,* 508-515.
- Singer, R. B., Strauss, D., & Shavelle, R. (1998). Comparative mortality in cerebral palsy patients in California, 1980-1996. *Journal of insurance medicine (New York, N.Y.), 30,* 240-246.
- Strauss, D., Shavelle, R., Reynolds, R., Rosenbloom, L., & Day, S. (2007). Survival in cerebral palsy in the last 20 years: signs of improvement? *Developmental medicine and child neurology, 49,* 86-92.

3 DISCUSSION

3.1 SC-GLYCO-06-01 MORTALITY RATE

Three deaths occurred during the 57.25 person-years observed in the Sc-GLYCO-06-01 trial. No patients in the ITT population died while taking the study drug. All three deaths occurred thirty days after the last study drug administration. As reporting of adverse events in this period is largely spontaneous, the sponsor was requested to verify the vital status of all patients thirty days post last study drug administration. The sponsor was able to verify vital status for all patients in the ITT population. No additional deaths were noted.

The mortality rate in the Sc-GLYCO-06-01 trial was 45.6/1,000 person-years (95% CI 14.7-141.4/1,000). The wide confidence interval for this mortality rate is not surprising given the low event rate and limited amount of person-years.

3.2 PUBLISHED CEREBRAL PALSY MORTALITY RATES

Three relevant cerebral palsy studies with mortality rates were identified by the literature search (Singer, Strauss, & Shavelle, 1998; Strauss, Shavelle, Reynolds, Rosenbloom, & Day, 2007; Blair, Watson, Badawi, & Stanley, 2001). One study was based on data from the Western Australian Cerebral Palsy Registry (Blair et al., 2001). The remaining two studies were both based on data from the California Department of Developmental Services (Singer et al., 1998; Strauss et al., 2007). These two studies presented mortality rates stratified by different factors, and thus were included in this review. For example, one study provided mortality rates for cerebral palsy patients 1-19 years of age stratified by quadriplegia (Singer et al., 1998); while the other provided mortality stratified by quadriplegia, ability to feed, and age (4-14 versus 15-60+) (Strauss et al., 2007) (Table 2).

3.3 QUALITATIVE COMPARISONS

Representative clinical features of patients in the Sc-GLYCO-06-01 trial and the selected studies are reported in Table 1. Overall, patients in the Sc-GLYCO-06-01 trial had more severe disease. More patients in the trial were quadriplegic, and markedly more patients in the trial had severe to profound intellectual impairment and required a feeding tube. These differences are not surprising given the patient population recruited for the trial and the fact that the selected studies reported on large clinically diverse cerebral palsy populations.

Table 1. Clinical Characteristics of Cerebral Palsy Studies

	N	Quadriplegia	Severe/Profound Intellectual Impairment	Feeding Tube Required
Sc-GLYCO-06-01	*137*	*57.7%*	*90.5%*	*51.1%*
Blair (2001)	2,014	16.8%	23.7%	N/A
Singer (1998)	38,044	49.9%	41.5%	7.6%
Strauss (2007)	58,698	N/A	N/A	6.0%

N/A: Not available, data not reported.

Mortality rates reported by each of the identified studies are listed in Table 2. The point estimate for the mortality rate in the Sc-GLYCO-06-01 trial was higher than any rate reported in the selected studies. However, the lower bound of the 95% confidence interval for the Sc-GLYCO-06-01 trial encompassed the mortality rates reported for more severe cerebral palsy patients in the selected studies.

More severe disability, indicated by use of feeding tubes or quadriplegia, was associated with an increased risk of death. This can be inferred from the stratified mortality rates in Table 2. This increased risk was quantified by Strauss et al who found that use of a feeding tube was associated with a 2.34 times increase in mortality in severe cerebral palsy patients and a 4.46 times increase in mortality in not-severe cerebral palsy patients (Strauss et al., 2007). In that analysis, patients were classified as severe if they were unable to crawl, creep, scoot, stand without support, or walk and were fed completely by others. The study from Blair and colleagues using data from the Western Australian Cerebral Palsy Register showed a similar relationship (Blair et al., 2001). Table 3 showed the increase in mortality for increasing levels of disability (as measured by an aggregate disability score). In multivariate analyses, each level of increasing intellectual impairment (minimal/mild/moderate/severe) was associated with a 2.14 times increase in mortality.

It is possible that the marked differences in the prevalence of quadriplegia, intellectual impairment, and use of feeding tubes explained the discrepancy between the mortality rate observed in the Sc-GLYCO-06-01 trial and the mortality rates reported in the selected studies. However, formal multivariate analyses to test this hypothesis were not conducted because of the Sc-GLYCO-06-01 trial's small sample size with respect to the other studies, and the lack of source data from the selected studies.

Table 2. Mortality Rates in Selected Cerebral Palsy Populations

	Study Period	Total Person-Years	Age Range	Stratification	Mortality Rate (/1000 person-years)	95% Confidence Interval
Sc-GLYCO-06-01	*2007-2008*	*57.25*	*3-18*	*None*	*45.6*	*(14.7-141.4)*
Blair (2001)	1956-1994	26,003	1-19	None	6.7	(6.0-7.7)
Singer (1998)	1980-1996	84,431	1-19	Not Quadriplegic	7.3	(6.8-7.9)
Singer (1998)	1980-1996	99,459	1-19	Quadriplegic	20.6	(19.7-21.5)
Strauss (2007)	1983-2002	24,996	4-14	Quadriplegic & Unable to feed	36.7	(34.3-39.1)
Strauss (2007)	1983-2002	111,761	4-14	Neither Quadriplegic nor Unable to feed	3.6	(3.3-4.0)
Strauss (2007)	1983-2002	34,657	15-60+	Quadriplegic & Unable to feed	39.4	(37.4-41.6)
Strauss (2007)	1983-2002	236,482	15-60+	Neither Quadriplegic nor Unable to feed	7.3	(6.9-7.6)

Table 3. Mortality in Cerebral Palsy by Disability Severity (Blair et al., 2001)

Table V: Crude mortality rates per 1000 person-years by overall disability score for children of 1 to 5 years and of 5 or more years

Overall disability score	*Crude mortality (nr deaths/person-years)*	
	1 to <5 y	*≥ 5 y*
1	0 (0/266)	0 (0/438)
2	0 (0/980)	0.73 (2/2740)
3	1.7 (2/1176)	1.23 (5/4053)
4	0.75 (1/1335)	1.11 (6/5400)
5	3.99 (3/752)	1.28 (4/3129)
6	6.23 (4/642)	3.1 (8/2578)
7	2.19 (1/456)	4.49 (8/1781)
8	22.2 (8/361)	8.5 (12/1411)
9	51.9 (28/540)	14.8 (26/1756)
10	46.7 (23/492)	18.4 (24/1304)
11	59.2 (14/237)	46(15/326)
12	79.8 (3/37.6)	8.2 (1/122)
Missing	0 (0/255)	3.3 (5/1516)
Total	11.56 (87/7526)	4.37 (116/26556)

4 CONCLUSIONS AND RECOMMENDATIONS

The mortality rate in Sc-GLYCO-06-01 was higher than other published estimates for cerebral palsy patients; however qualitative comparisons to peer-reviewed mortality rates did not provide sufficient evidence to unequivocally conclude that the Sc-GLYCO-06-01 mortality rate was different than the expected background rate. Two key characteristics of the Sc-GLYCO-06-01 trial prevented a more unequivocal analysis: 1) the trial was not powered to estimate a mortality rate with reasonable precision, and 2) the trial's distribution of neurologic diagnoses and level of disability was dissimilar to the distributions in other cerebral palsy studies.

As previously stated, the mortality rate estimate for the Sc-GLYCO-06-01 trial was imprecise. With only three events, the 24 week follow-up period did not provide a sufficient amount of person-time to construct a more informative 95% confidence interval. Thus, although the point estimate was greater than any estimate in the selected literature, it could not be definitively concluded that the rate observed in the Sc-GLYCO-06-01 trial was different than the true background rate in cerebral palsy, especially in more disabled cerebral palsy patients. However, one could reasonably argue that a statement of no difference would be a type-II error given the imprecision of the estimated mortality rate in the Sc-GLYCO-06-01 trial. As such, the mortality rate in the Sc-GLYCO-06-01 trial may be greater than the true population mortality rate, but the trial did not have the statistical power needed to detect such a difference.

Regardless of the potential power issues described above, formal statistical tests were not conducted due to the lack a data from a sample with similar clinical and demographic characteristics. The majority of Sc-GLYCO-06-01 patients were spastic quadriplegic cerebral palsy patients, with mental retardation and speech impairments. However, 29.9% of ITT population had a neurologic condition other than cerebral palsy. Regardless of their neurologic condition, 66.4% of the patients had oral feeding problems and 51% of the patients used a feeding

tube. Published reports from developmental disability cohorts did not contain enough descriptive data to assess whether their subjects were similar to the ITT population of the Sc-GLYCO-06-01 trial in terms of neurologic diagnoses and disability severity. Given that 70.1% of the ITT population had cerebral palsy and all three events occurred in cerebral palsy patients, it was decided that the best available comparison data would come from cerebral palsy studies. It must be recognized that qualitative comparisons between the mortality rate in the Sc-GLYCO-06-01 trial and the published rates from other cerebral palsy studies assumed that the mortality rate in cerebral palsy was representative of the mortality rate for all other neurodevelopmental disorders included in the trial. However, it would be very difficult to assess the expected mortality in these other neurologic diagnoses without a better description of their clinical severity. As such, it was decided that formal statistical tests or probability statements about the degree to which the observed mortality rate differed from the expected mortality rate would be inappropriate.

Unfortunately, even the limited data from the selected cerebral palsy studies did not provide mortality rate estimates which were easily compared to the mortality rate observed in the Sc-GLYCO-06-01 trial. The published cerebral palsy mortality rates were often stratified by quadriplegia; however the distribution of mental retardation, feeding problems and feeding tube use within each quadriplegia stratum was not provided (Blair et al., 2001; Singer et al., 1998; Strauss et al., 2007). The multivariate distribution of these variables was essential for accurate comparisons since disability severity was generally correlated with increased mortality. Unfortunately, the SC-GLYCO-06-01 mortality rate could not be stratified by quadriplegia and other forms of disability due to the trial's small sample size and low event rate. Thus, it was very difficult to make an assessment on how similar the stratified rates found in the literature were to the rate in the Sc-GLYCO-06-01 trial. While, it is possible that the high mortality rate in the Sc-GLYCO-06-01 trial is explained by the severe disability in the ITT population, the limitations described above precluded a more definitive assessment.

For the reasons explained above, DEPI does not recommend that comparisons to published cerebral palsy mortality rates be used to determine if the three deaths observed in the Sc-GLYCO-06-01 trial were due to glycopyrrolate or were just the expected number of deaths given the background mortality rate in this population. Other data from the clinical development program or the post-marketing period may better address this question.

5 REFERENCES

Blair, E., Watson, L., Badawi, N., & Stanley, F. J. (2001). Life expectancy among people with cerebral palsy in Western Australia. *Developmental medicine and child neurology, 43,* 508-515.

Singer, R. B., Strauss, D., & Shavelle, R. (1998). Comparative mortality in cerebral palsy patients in California, 1980-1996. *Journal of insurance medicine (New York, N.Y.), 30,* 240-246.

Strauss, D., Shavelle, R., Reynolds, R., Rosenbloom, L., & Day, S. (2007). Survival in cerebral palsy in the last 20 years: signs of improvement? *Developmental medicine and child neurology, 49,* 86-92.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

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Department of Health and Human Services
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Date:	April 29, 2010
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Through:	Ann McMahon, M.D., Deputy Director Division of Pharmacovigilance I (DPV I) and Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader, Division of Pharmacovigilance I (DPV I)
From:	Namita Kothary, Pharm.D., Safety Evaluator Division of Pharmacovigilance I (DPV I)
Subject:	All adverse events in children 0-18 years of age
Drug Name(s):	Glycopyrrolate
Application Type/Number:	NDA 22-571 *(not approved, under review by DDDP)* NDA 12-827 *(oral tablets)* NDAs 17-558, 14-764 *(injectable)* ANDAs 40-568, 40-653, 40-821, 40-836, 40-844, 40-847, 81-169, 85-562, 85-563, 86-178, 86-900, 86-902, 86-947, 88-475, 89-335, 89-393, 89-397
Applicant/sponsor:	Sciele Pharma Inc.
OSE RCM #:	2010-538

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EXECUTIVE SUMMARY

The Division of Dermatology and Dental Products (DDDP) is reviewing NDA 22-571, TRADENAME (glycopyrrolate) Oral Solution for the treatment of (b) (4) drooling in children 3 years and older with cerebral palsy (CP), (b) (4), or other neurologic conditions. Glycopyrrolate (oral tablets and injectable) is available in the US as Robinul, Robinul Forte, and multiple generics. Initially, DDDP requested that we verify the sponsor's assessment of adverse events associated with glycopyrrolate by searching the Adverse Event Reporting System (AERS) database for adverse events associated with the use of all formulations of glycopyrrolate in children 0-18 years. Following additional discussions with the DDDP Medical Officer, we decided to provide a more in-depth analysis of the following: 1. cases with an outcome of death for all formulations, 2. cases of tachycardia / supraventricular or ventricular arrhythmia for all formulations, and 3. adverse events associated with oral glycopyrrolate (NDA 22-571 is for an oral formulation).

We identified 40 adverse event cases associated with any formulation of glycopyrrolate. Overall, the adverse events reported with glycopyrrolate are consistent with anticholinergic effects. The specific role that glycopyrrolate played in the two cases with an outcome of death is unclear since multiple medications were administered at the same time. We identified 12 cases of tachycardia / supraventricular and ventricular arrhythmias that suggest an association between the events and glycopyrrolate based on the number of cases (12/40, 30%) and temporal relationship between drug administration and the events; however, tachycardia is already included in both product labels. We identified 12 cases of adverse events associated with the use of oral glycopyrrolate (by mouth or gastrostomy tube) in children 0-18 years old. The majority of these cases reported adverse events that are not in the oral glycopyrrolate label; however, it is difficult to determine the role glycopyrrolate played in these cases because the narratives generally contained limited information and the adverse events were reported in only one or two cases each. Additionally, many of the reported events are consistent with anticholinergic side effects, even though they are not specifically included in the product label.

Perhaps based in part on the limited number of cases in this series, variable quality and quantity of information provided, and the under-reporting to spontaneous reporting systems such as AERS (particularly for older drugs or drugs where the adverse event profile is accepted), we did not identify any new significant safety concerns associated with the use of any formulation of glycopyrrolate in children 0-18 years old.

Based on the post-marketing cases discussed in this review and safety information in the glycopyrrolate product labels, DPV I has no additional labeling recommendations at this time provided that the label for NDA 22-571 reflects currently available safety information.

1 BACKGROUND

This review describes post-marketing adverse event cases in the Adverse Event Reporting System (AERS) database associated with the use of glycopyrrolate in children 0-18 years, with a focus on cases with an outcome of death, cases of tachycardia / supraventricular or ventricular arrhythmia, and adverse events associated with oral glycopyrrolate.

1.1 INTRODUCTION

The Division of Dermatology and Dental Products (DDDP) is reviewing NDA 22-571, TRADENAME (glycopyrrolate) Oral Solution for the treatment of pathologic drooling in children 3 years and older with cerebral palsy (CP), mental retardation, or other neurologic conditions. Glycopyrrolate (oral tablets and injectable) is available in the US as Robinul, Robinul Forte, and multiple generics.[1,2] Although these formulations are not FDA approved for drooling, a number of literature articles describe the off-label use of glycopyrrolate to treat drooling in children with CP.[3-8]

In the submission for NDA 22-571, the sponsor states, "no AEs were found in the Sciele Pharma Inc. Drug Safety Database 2001-2007 for children (under 18 years of age) who received Robinul tablets…. The FDA AERS was examined for AEs for which glycopyrrolate was the primary or secondary suspect drug, and results for patients of all ages are provided in the [Integrated Summary of Safety]. There were no AEs identified in children for which glycopyrrolate, glycopyrronuim bromide, or Robinul was the primary suspect drug in 2005 through 2007. However, in the third quarter of 2007, Robinul was listed as the secondary suspect drug for AEs of aggression and sleep disorder in an 11-year old female."[9]

DDDP requested that we verify the sponsor's assessment of adverse events associated with glycopyrrolate by searching the Adverse Event Reporting System (AERS) database for adverse events associated with the use of all formulations of glycopyrrolate in children 0-18 years. It is unclear why the sponsor only included AERS reports from 2005-2007; therefore, we included all adverse events reported to AERS for this age group.

Following additional discussions with the DDDP Medical Officer, we decided to provide a more in-depth analysis of the following:

1. Cases with an outcome of death for all formulations
2. Cases of tachycardia / supraventricular and ventricular arrhythmias for all formulations *(DDDP consulted the Division of Cardio-Renal Products (DCRP) in reference to a potential QT/QTc issue. DCRP requested a search of AERS to identify relevant post-marketing reports.)*
3. Adverse events associated with oral glycopyrrolate *(NDA 22-571 is for an oral formulation)*

1.2 REGULATORY HISTORY

The FDA approved glycopyrrolate 1 mg and 2 mg oral tablets (NDA 12-827, Robinul and Robinul Forte) on August 11, 1961 and glycopyrrolate 0.2 mg/mL injectable (NDAs 17-558, 14-764, Robinul) on February 6, 1975. Both formulations are FDA approved as adjunctive therapy

for peptic ulcers. The injectable formulation is also FDA approved as a preoperative and intraoperative antimuscarinic agent.[1,2]

1.3 PRODUCT LABELING

Glycopyrrolate is a synthetic anticholinergic (antimuscarinic) agent. It inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation.[1,2]

The safety and efficacy in pediatric patients has not been established for either formulation of glycopyrrolate. However, the injectable glycopyrrolate label provides dosing information for use during anesthesia in children over one month old. Glycopyrrolate tablets are not recommended for patients less than 12 years old. The injectable formulation contains benzyl alcohol and should not be used in neonates less than one month old due to the risk of toxicity and death. In general, infants and young children may be more susceptible to the toxic effects of anticholinergics.[1,2]

There are a number of contraindications, warning, precautions, and adverse events associated with glycopyrrolate. The majority of these are associated with its activity as an anticholinergic agent. Appendix A contains additional labeling regarding the indications, pediatric use, and safety information.

2 MATERIAL REVIEWED

We searched AERS on March 9, 2010 for all adverse event reports in children 0-18 years old, regardless of seriousness, associated with glycopyrrolate using the following criteria:

- Time period: reports in AERS as of March 9, 2010
- Age limits: 0 to 18 years old
- Drug terms: glycopyrrolate and Robinul (including associated trade, active ingredient, and verbatim names)

The AERS search retrieved 364 total adverse event reports associated with glycopyrrolate; of which 44 (12%) were reported in children 0-18 years old. We excluded four cases because they were duplicate reports (3) or occurred in a patient over 18 years old (1).

Section 3.1 describes adverse events in children 0-18 years old associated with any formulation of glycopyrrolate (n=40), cases with an outcome of death (n=2), and cases of tachycardia / supraventricular or ventricular arrhythmia (n=12).

Section 3.2 describes cases that reported oral or gastrostomy tube (GT) routes of administration for glycopyrrolate in children 0-18 years old (n=12).

3 RESULTS

3.1 ADVERSE EVENTS ASSOCIATED WITH ANY FORMULATION OF GLYCOPYRROLATE (N=40)

Overview of all adverse events (n=40)

Table 1 summarizes the labeling status for adverse events in children 0-18 years old associated with any formulation of glycopyrrolate and reported in at least two AERS cases. We reconciled duplicate reports and identified 1. cases with an outcome of death, 2. cases of tachycardia / supraventricular or ventricular arrhythmia, and 3. adverse events associated with oral glycopyrrolate. However, a full hands-on analysis was not conducted for the remaining cases (i.e. we did not assess the cases for temporal relationship, causality, etc.). Appendix B contains the AERS ISR numbers for all 40 cases.

Table 1. Preferred Terms reported in ≥ 2 AERS cases in children 0-18 years old associated with any formulation of glycopyrrolate, from reports in AERS as of March 9, 2010 (n=40)

MedDRA Preferred term	N (%)	Label status*[1,2]	
1. Pyrexia	7 (18%)	Oral: L- W (fever)	Inj: L- W (heat prostration), OD
2. Drug Ineffective	6 (15%)	n/a	
3. Tachycardia	5 (13%)	Oral: L- AR	Inj: L- P, AR
4. Vasodilatation	4 (10%)	NL	
5. Urinary Retention	3 (8%)	L- AR	
6. Vomiting	3 (8%)	L- AR	
7. Pulmonary Oedema	3 (8%)	NL	
8. Blood Glucose Increased	2 (5%)	NL	
9. Bradycardia	2 (5%)	Oral: NL	Inj: L- PM
10. Heart Rate Increased	2 (5%)	Oral: L- AR (tachycardia)	Inj: L- P, AR (tachycardia)
11. Hypertension	2 (5%)	Oral: NL	Inj: L- PM
12. Hypotension	2 (5%)	Oral: L- OD	Inj: L- PM
13. Mydriasis	2 (5%)	Oral: L- AR (dilation of the pupil), OD	Inj: L- AR
14. Oliguria	2 (5%)	L- AR (urinary hesitancy and retention)	
15. Oxygen Saturation Decreased	2 (5%)	NL	
16. Sinus Tachycardia	2 (5%)	Oral: L- AR (tachycardia)	Inj: L- P, AR (tachycardia)
17. Urticaria	2 (5%)	L- AR	

*L=Labeled (verbatim term from the label included if different than the MedDRA PT), NL=Not labeled, W= Warning, P=Precautions, AR= Adverse Reactions, PM= Post-Marketing, OD= Overdose

Cases with an outcome of death (n=2)

ISR 3164835, US (1998): A 5-year-old male received anesthesia with 1 mL oral midazolam, 0.02 mg IV fentanyl, 0.05 mg IV glycopyrrolate, and 20 mg IV methohexital prior to a dental procedure. Approximately 5-10 minutes after he received fentanyl, glycopyrrolate, and methohexital, he experienced respiratory depression (PO_2=70) with bradycardia (heart rate=40 bpm, blood pressure=60/40). He died approximately 4.5 hours after administration of the anesthesia medications despite treatment with flumazenil, epinephrine, atropine, oxygen, naloxone, dopamine and bicarbonate, epinephrine and calcium, methylprednisolone, and resuscitative efforts both in the dental office and in the emergency room. The autopsy report indicated the cause of death was "an apparent idiosyncratic reaction to the sedation medications [glycopyrrolate, midazolam, and methohexital]."

ISR 3164835, US (1998): A 18-year-old female received anesthesia with 0.2 mg IV glycopyrrolate, 5 mg "Curare," 20 mg ketamine, and 140 mg pentothal for a Cesarean section. Prior to the procedure, she received ritodrine for approximately 36 hours due to premature labor. During the Cesarean section, she received valium, fentanyl, and pancuronium. The reporter stated, "surgery and anesthesia were uncomplicated." However, after the surgery, she experienced difficulty breathing, low blood pressure, no palpable pulse, and was pale and unresponsive. She was treated with oxygen, normal saline, dopamine, bicarbonate, calcium gluconate, calcium chloride, atropine, propanolol, isoproterenol, epinephrine, intracardiac epinephrine; CPR was initiated and she was intubated. Four hours after the surgery, her blood pressure improved to 110/70; however, EKG showed supraventricular tachycardia. Subsequently, she received fresh frozen plasma due to suspected disseminated intravascular coagulation. A pulmonary arteriogram performed seven hours after surgery confirmed two large defects and she was diagnosed "with multiple pulmonary emboli with resulting respiratory arrest." She died approximately 38 hours after the Cesarean section.

Cases of tachycardia / supraventricular and ventricular arrhythmias (n=12)

We identified 12 cases that reported adverse events related to tachycardia / supraventricular and ventricular arrhythmias in children 0-18 years old who used any formulation of glycopyrrolate (Table 2). One case was reported from a study and one case was reported from the literature; both of these cases were also reported to AERS. Appendix C contains summaries of the individual cases in the event that DCRP needs additional details for their analysis.

Table 2. Characteristics of cases in which tachycardia / supraventricular and ventricular arrhythmias was associated with any formulation of glycopyrrolate, from reports in AERS as of March 9, 2010 (n=12)

Origin	US (12)
Report type	Expedited (6) Direct (4) Periodic (2)
Initial FDA received date	1977 (1) 1983 (3) 1984 (1) 1989 (1) 1994 (1) 1996 (1) 2002 (1) 2004 (1) 2007 (1) 2008 (1)
Gender	Male (6) Female (5) NS (1)
Age (years)	Mean: 9 Median: 9 Range: 0.2 – 18 years
Route of Administration	IV (5) IM (1) Oral/GT (5) NS (1)
Duration of therapy (n=11)	Mean: 16 days Median: 1 day Range: 1 dose – at least 4.8 months
Time to event from start of therapy (n=11)	Mean: 17 days Median: same day as glycopyrrolate administration Range: 1 minute – 4.6 months
Indications	Decrease secretions, including mucous, saliva, etc. (4) Surgery (4) Hyperhidrosis (1) Anticholinergic (1) Pneumonia (1) NS (1)
Adverse events *(Note: tachycardia is listed the oral and injectable glycopyrrolate labels, the other events are not)*	Tachycardia (6) Increased heart rate or pulse (3) Sinus tachycardia (1) Bigeminy with short runs of ventricular tachycardia (1) Sinus tachycardia with ST segment elevations, T-wave abnormality, and prolonged QT (1)
Primary outcome	Life-threatening (2) Hospitalization (5) Required intervention (1) Other serious (4)

NS = Not stated

3.2 ORAL ROUTE OF ADMINISTRATION (N=12)

Table 3 summarizes the 12 cases in children 0-18 years old who used glycopyrrolate administered by mouth or GT. Five of the 12 cases reported events related to tachycardia or increased heart rate and were captured in the search for cases of tachycardia / supraventricular and ventricular arrhythmias described above.

Table 3. Characteristics of cases in which glycopyrrolate was administered by mouth or GT, from marketing to March 9, 2010 (n=12)	
Origin	US (12)
Report type	Expedited (5) Periodic (4) Direct (3)
Initial FDA received date	1979 (1) 1989 (1) 1990 (1) 1994 (3) 1996 (1) 1998 (1) 2002 (1) 2003 (1) 2007 (1) 2008 (1)
Gender	Male (6) Female (5) NS (1)
Age (years)	Mean: 9 Median: 7 Range: 0.58 – 18 years
Duration of therapy (n=10)	Mean: 2.2 months Median: 1.4 months Range: 1 day – 7-9 months
Time to event from start of therapy (n=8)	Mean: 27 days Median: 8 days Range: 2 hours – 4.6 months
Indications	Decrease secretions, including mucous, saliva, etc. (7) Hyperhidrosis (1) Irritable bowel syndrome, possible (1) Pneumonia (1) "[illegible text] salivary secretions / lack of swallow mechanism" (1) NS (1)
Adverse events, by body system* *(Italics indicate events included in the oral glycopyrrolate label)*	Cardiovascular (6 cases): hypertension (1), hypertension and *tachycardia* (1), *tachycardia* (1), *sinus tachycardia* (1), *high pulse* (1), *rapid heart rate* (1) Renal (5 cases): *oliguria* (2), *urinary retention* (1), staphylococcal and enterococcus urinary tract infection (1), increased serum creatinine and renal failure (1) Laboratory tests (3 cases): oxygen saturation decreased (2), oxygen saturation decreased and increased white count and increased lymphocyte count (1) Respiratory (2 cases): respiratory distress and pulmonary hypertension and pseudomonas pneumonia and lung scarring (1), red/rough/painful throat and cough with bloody sputum and shortness of breath and pneumothorax and emphysema and bronchoscopy showed "very dry tissues, burned tissues" (1) Dermatologic (1 case): *urticaria* and angioedema (1) Hepatic (1 case): increased PT, APTT, and liver enzymes (1) Gastrointestinal (1 case): *constipation* (1) Nervous System (1 case): grand mal seizures (1) Other (7 cases): *"anticholinergic effects"* (1), loss of appetite and drug ineffective (1), *fever* (1), irritability and crying (1), drug overdose and pain and dehydration and fatigue (1), *fever* and restlessness and discomfort (1), facial flushing (1)
Primary outcome	Life-threatening (1) Hospitalization (5) Required intervention (1) Other serious (2) Non-serious outcome (3)

*More than one is possible per case
NS = Not stated

4 DISCUSSION

We identified 40 adverse event cases associated with any formulation of glycopyrrolate, including the case of aggression and sleep disorder in an 11-year-old female mentioned by the sponsor in their submission. Our search results and subsequent assessment are discrepant from the sponsor's assessment; however, one reason may be that we searched for all adverse events in AERS as of March 9, 2010 instead of restricting the search to 2005-2007. Additionally, since glycopyrrolate is available as both brand and generic, multiple manufacturers may report adverse events to AERS.

4.1 ADVERSE EVENTS ASSOCIATED WITH ANY FORMULATION OF GLYCOPYROLLATE (N=40)

Overview of all adverse events (n=40)

Overall, the adverse events reported with glycopyrrolate are consistent with anticholinergic effects. This is not surprising given that glycopyrrolate is an anticholinergic agent that may affect multiple organ systems. Seventeen adverse events were reported in at least two cases (see Table 1). The top three reported adverse events are:

1. Pyrexia (included in the Warnings section of both labels)
2. Drug ineffective (not labeled, but expected given that no drug is effective in all patients)
3. Tachycardia (included in the Adverse Reactions section of both labels and the Precautions section of the injectable label)

The majority of reported adverse events are in the both the oral and injectable labels (10/17). Additionally, two adverse events are only in the injectable label (bradycardia and hypertension). The two cases of bradycardia reported the use of injectable glycopyrrolate, and the label reflects this. However, the two cases of hypertension reported the use of oral glycopyrrolate. Although the oral glycopyrrolate label does not reflect this, the cases do not support a clear association between the drug and event. The five remaining adverse events (drug ineffective, vasodilatation, pulmonary oedema, blood glucose increased, oxygen saturation decreased) are not included in either product label; however, the cases do not support a clear association between the drug and events.

Cases with an outcome of death (n=2)

The specific role that glycopyrrolate played in the two cases with an outcome of death is unclear since multiple medications were administered at the same time. Death occurred approximately 4.5 hours and 38 hours after administration of injectable glycopyrrolate for anesthesia. However, both patients received multiple medications to induce and maintain anesthesia at the same time as glycopyrrolate; therefore, it is difficult to attribute the events to one agent in particular.

Cases of tachycardia / supraventricular and ventricular arrhythmias (n=12)

We identified 12 cases of tachycardia / supraventricular and ventricular arrhythmias that suggest an association between the events and glycopyrrolate based on the number of cases (12/40, 30%) and temporal relationship between drug administration and the events; however, tachycardia is

already included in both product labels (see Appendix C for case summaries). Additionally, tachycardia associated with anticholinergic effects has been reported in the literature.[10] One case reported a possible medication error in which succinylcholine may have been given instead of glycopyrrolate; however, the reporter stated that there is no way to confirm which drug was administered. Additionally, two cases reported that the events were more likely related to succinylcholine. However, since we cannot definitively conclude that glycopyrrolate did not play a role in these cases, we included these three cases in the analysis.

The adverse events occurred following the use of injectable glycopyrrolate (7) and oral glycopyrrolate (5); however, no trends were apparent based on the route of administration. All 12 cases reported events related to tachycardia or increased heart rate, with values ranging from 110 to 220 (n=8). One of the 12 cases also reported ST segment elevation, T-wave abnormality, and prolonged QT in addition to sinus tachycardia. In nine of the 12 cases, tachycardia occurred the same day as glycopyrrolate administration. Glycopyrrolate was discontinued in all nine cases (same day-8, unknown date-1) and the tachycardia improved following treatment in eight of the cases; the outcome was unknown in the ninth case. In the remaining three cases, tachycardia occurred two days, ~2.3 months, and ~4.6 months after starting therapy; the tachycardia improved following treatment in all three cases. Two of the 12 cases reported tachycardia following an accidental overdose; both cases reported that the adverse events resolved after an unspecified amount of time. One case also reported a positive rechallenge of the tachycardia. Of note, eight of the 12 cases reported the use of other medications associated with tachycardia; these cases are indicated by an asterisk next to the AERS ISR number in Appendix C.

4.2 ORAL ROUTE OF ADMINISTRATION (N=12)

We identified 12 cases of adverse events associated with the use of oral glycopyrrolate (by mouth or GT) in children 0-18 years old. The majority of cases reported adverse events that are not in the oral glycopyrrolate label; however, it is difficult to determine the role glycopyrrolate played in these cases because the narratives generally contained limited information and the adverse events were reported in only one or two cases each. Additionally, many of the reported events are consistent with anticholinergic side effects, even though they are not specifically included in the product label.[3,10]

Adverse events affecting the cardiovascular and/or renal system were the most commonly reported events (8/12 cases). Six cases reported cardiovascular adverse events. One of the cases reported hypertension, an increased serum creatinine, and renal failure that was more likely related to treatment with multiple courses of cisplatin, which has a boxed warning for renal toxicity.[11] The remaining five cases reported events related to tachycardia, which is listed in the Adverse Reactions section of the oral glycopyrrolate label (see Section 4.1 for more details). Five cases reported adverse events affecting the renal system. Three of these cases described urinary disorders (oliguria-2, urinary retention-1), which are listed in the Adverse Reactions section of the oral glycopyrrolate label. Of the remaining two cases, one reported renal failure possibly related to cisplatin toxicity as described above and the second reported a urinary tract infection. Three cases reported both cardiovascular and renal adverse events.

The remaining four cases did not suggest any trends; therefore, it is difficult to draw conclusions from these cases. The reported events in these four cases were: 1. grand mal seizures, 2. urticaria and angioedema, 3. loss of appetite and lack of effect, and 4. increased PT, APTT, and liver enzymes (reported as "hepatitis unrelated to [glycopyrrolate]") and "anticholinergic effects."

None of the 12 cases reported using oral glycopyrrolate for an FDA approved indication, which may be one reason why the reported formulations and dosing varied considerably. Nine of the 12 cases provided information on which formulation of glycopyrrolate was used (tablets-6, injectable-2, syrup-1). Of the ten cases that provided dosing information, no two cases appeared to have the same dose of glycopyrrolate. The oral doses ranged from 0.2 mg to 5 mg three times daily (n=7). The dose for the syrup was 12.5 mL three times a day. The doses for the two injectable formulations were 0.45 mL and 5 mg/mL. The case of a 2-year-old male who received an accidental overdose of glycopyrrolate (5 mg/mL instead of 1 mg/5mL of the injectable formulation given via GT) highlights the potential for error associated with off label use. Of note, a literature search also failed to show an agreed upon dosing regimen for oral glycopyrrolate. The dosing recommendations in the literature ranged from 0.01-0.14 mg/kg/dose three to four times a day to 0.6-3 mg three times a day.[4-8]

5 CONCLUSIONS

Perhaps based in part on the limited number of cases in this series, variable quality and quantity of information provided, and the under-reporting to spontaneous reporting systems such as AERS (particularly for older drugs or drugs where the adverse event profile is accepted), we did not identify any new significant safety concerns associated with the use of any formulation of glycopyrrolate in children 0-18 years old.

6 RECOMMENDATIONS

Based on the post-marketing cases discussed in this review and safety information in the glycopyrrolate product labels, DPV I has no additional labeling recommendations at this time provided that the label for NDA 22-571 reflects currently available safety information.

7 REFERENCES

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8 APPENDICES

8.1 Appendix A. Summary of information from glycopyrrolate product labels
8.2 Appendix B. AERS cases included in review (n=39)
8.3 Appendix C. Summary of cases in which tachycardia was associated with any formulation of glycopyrrolate, from marketing to March 9, 2010 (n=9)

8.1 APPENDIX A. SUMMARY OF INFORMATION FROM GLYCOPYRROLATE PRODUCT LABELS

	Glycopyrrolate oral tablets[1]	Glycopyrrolate injectable[2]
Indication	• **Peptic Ulcer:** as adjunctive therapy	• **Anesthesia (preoperative):** to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation • **Anesthesia (intraoperative):** to counteract surgically or drug induced or vagal reflexes associated arrhythmias; protect against peripheral muscarinic effects of cholinergic agents given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants • **Peptic Ulcer:** as adjunctive therapy, when rapid anticholinergic effect is desired or when oral medication is not tolerated.
Pediatric Use	• Safety and efficacy in pediatric patients have not been established • Not recommended for pediatric patients under the age of 12	• Safety and effectiveness in <16 year olds not established • Should not be used in neonates < 1 month of age due to the benzyl alcohol content • **Anesthesia:** dosing provided for ≥1 month old • **Peptic Ulcer:** not recommended for pediatric patients • Pediatric patients may experience dysrhythmias; pediatric patients taking large doses of anticholinergics may experience a paradoxical reaction characterized by hyperexcitability • Infants, patients with Down's syndrome, and pediatric patients with spastic paralysis or brain damage may experience an increased response to anticholinergics. Infants and young children are especially susceptible to the toxic effects of anticholinergics.
Contraindications	• Hypersensitivity to glycopyrrolate • Glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis	• Hypersensitivity to glycopyrrolate or any inactive ingredient • Peptic ulcer indication- glaucoma, obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis
Warnings	• In the presence of a high environmental temperature, heat prostration (fever and heat stroke due to decreased sweating). • Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly	• This drug should be used with great caution, if at all, in patients with glaucoma. • Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. • Drowsiness or blurred vision. The patient should be cautioned regarding

	harmful. • Drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery, or performing hazardous work while taking this drug. • Theoretically, with overdosage, a curare-like action may occur, i.e., neuro-muscular blockade leading to muscular weakness and possible paralysis.	activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. • In the presence of fever, high environmental temperature and/or during physical exercise, heat prostration can occur with use of anticholinergic agents including glycopyrrolate (due to decreased sweating), particularly in children and the elderly. • Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with ROBINUL Injection would be inappropriate and possibly harmful.
Precautions	• Elderly • Patients with autonomic neuropathy, hepatic or renal disease, ulcerative colitis, hyperthyroidism, coronary heart disease, congestive heart failure, tachycardia, cardiac tachyarrhythmias, hypertension, prostatic hypertrophy, hiatal hernia (associated with reflux esophagitis)	• Elderly • Patients with autonomic neuropathy, hepatic or renal disease, ulcerative colitis, hyperthyroidism, coronary artery disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension, prostatic hypertrophy, hiatal hernia, gastric ulcer (delay in emptying due to antral statis)
Adverse Reactions	• Xerostomia, decreased sweating, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, dilation of the pupil, cycloplegia, increased ocular tension, loss of taste, headaches, nervousness, mental confusion, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, constipation, bloated feeling, impotence, suppression of lactation, severe allergic reaction or drug idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations.	• Xerostomia, urinary hesitancy and retention, blurred vision and photophobia due to mydriasis, cycloplegia, increased ocular tension, tachycardia, palpitation, decreased sweating, loss of taste, headache, nervousness, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, impotence, suppression of lactation, constipation, bloated feeling, severe allergic reactions including anaphylactic / anaphylactoid reactions, hypersensitivity, urticaria, pruritus, dry skin, and other dermal manifestations, some degree of mental confusion and/or excitement, especially in elderly persons. • Post-marketing experience: malignant hyperthermia, cardiac arrhythmias (including bradycardia, ventricular tachycardia, ventricular fibrillation), cardiac arrest, hypertension, hypotension, seizures, respiratory arrest, heart block and QTc interval prolongation associated with the combined use of glycopyrrolate and an anticholinesterase. • Injection site reactions including pruritus, edema, erythema, and pain have also been reported.
Other	• Recommended maximum daily dose is 8 mg	

8.2 APPENDIX B. AERS CASES INCLUDED IN REVIEW (N=40)

AERS ISR #	IV glycopyrrolate (n=28)	Oral glycopyrrolate (n=12)	Outcome of death (n=2)	Tachycardia / supraventricular and ventricular arrhythmias (n=12)
1. 6782	X			
2. 92101	X			X
3. 92972	X			
4. 146974	X		X	
5. 156783	X			X
6. 156919	X			X
7. 156920	X			X
8. 156948	X			
9. 180899	X			X
10. 578254		X		
11. 579203	X			
12. 607059	X			X
13. 645620	X			
14. 654050		X		
15. 682491	X			
16. 682617	X			
17. 682724	X			
18. 682725	X			
19. 682878	X			
20. 923604	X			
21. 1418308		X		
22. 1437646		X		
23. 1451537		X		X
24. 1947427		X		X
25. 1986836	X			
26. 3056638		X		
27. 3164835	X		X	
28. 3894292		X		X
29. 4127732		X		
30. 4187880	X			
31. 4495805	X			X
32. 5427513	X			
33. 5578846		X		X
34. 5943546		X		X
35. 6181074	X			
36. 70006491	X			
37. 70006493	X			
38. 70007357	X			
39. 70011581		X		
40. 70011769	X			

8.3 APPENDIX C. SUMMARY OF CASES IN WHICH TACHYCARDIA WAS ASSOCIATED WITH ANY FORMULATION OF GLYCOPYRROLATE, FROM MARKETING TO MARCH 9, 2010 (N=12)

*Cases that reported the use of other medications associated with tachycardia.

ISR 92101*, US (1977): A 7-year-old male received one dose of glycopyrrolate 0.1 mg IM as an anticholinergic agent. He also received meperidine, pentobarbital, oxygen, nitrous oxide, and halothane for an unspecified surgery. The same day as the surgery, he experienced ***bigeminy with short runs of ventricular tachycardia***. He was switched to enflurane and went into regular sinus rhythm. Concomitant medications included methylphenidate.

ISR 156783, US (1983): A 9-month-old child (gender unspecified) received one dose of glycopyrrolate 0.1 mg/kg injectable (route of administration unknown) for an unknown indication. The dose for glycopyrrolate was miscalculated resulting in an ***accidental overdose***. The same day as glycopyrrolate was administered, the child experienced ***tachycardia (160-190)***. The child was hospitalized and recovered after an unspecified amount of time.

ISR 156919*, US (1983): A 14-year-old female received one dose of glycopyrrolate IV while hospitalized for a tonsillectomy. She also received hydroxyzine, meperidine, sodium pentothal, succinylcholine, fentanyl, and lidocaine for the surgery. The same day as the surgery, she experienced a number of adverse events including ***tachycardia with a systolic blood pressure of 140-160, adult respiratory distress syndrome, dilated pupils, face flushed, scanty urine output, hypotension (90/50), and fever 101.4 F***. She required unspecified treatment and recovered after an unspecified amount of time. Concomitant medications included digoxin, furosemide, morphine sulfate, aminophylline, and sodium bicarbonate. Medical history included possible mononucleosis. The reporter indicated the events were more likely related to succinylcholine.

ISR 156920*, US (1983): A 16-year-old male received one dose of glycopyrrolate IV for while hospitalized for a fractured nasal bone. He also received hydroxyzine, meperidine, succinylcholine, and fentanyl for the surgery. The same day as the surgery, he experienced a number of adverse events including ***tachycardia (>140) and an increased systolic blood pressure of 220, "stiff lung on ventilation," acute pulmonary edema, rales, fever (39.4 C) and was cyanotic and combative with warm skin***. She required unspecified treatment and recovered after an unspecified amount of time. Concomitant medications included digoxin, furosemide, morphine sulfate, diazepam, and sodium bicarbonate. The reporter indicated the events were more likely related to succinylcholine.

ISR 180899*, US (1984): A 12-year-old female received one dose of glycopyrrolate 0.2 mg IV during an appendectomy. Within 1 minute of administration, she was ***apneic and cyanotic with "BP↑170 P 150."*** The duration was 3-4 minutes and she was ventilated during that time. The reporter indicated she may have received succinylcholine by mistake, but that there was no way to know.

ISR 607059*, US (1989): A 2-month-old male received two doses of glycopyrrolate 0.05 mg IV for one day to reduce secretions after surgery for bilateral inguinal hernia repair. He also received caffeine IV post-operatively. The same day as both drugs were administered, he experienced ***restlessness, tachycardia (180-220), and vomiting***. The eventual clinical outcome is unknown.

ISR 1451537, US (1994): A 6-year-old female received glycopyrrolate 5 mg three times daily to treat pneumonia. An unspecified amount of time after starting glycopyrrolate, she experienced tachycardia. The following day, the glycopyrrolate dose was decreased to 0.25 mg three times daily. The day after the dose was decreased, she experienced ***facial flushing, tachycardia, and hypertension*** two hours after glycopyrrolate administration. Glycopyrrolate was discontinued on an unknown date and she recovered following unspecified treatment.

ISR 1947427, US (1996): A 7-month-old male received one dose of glycopyrrolate 0.2 mg via GT for increased secretions. The same day that glycopyrrolate was given, he experienced a ***fever (up to 105.4 F) and tachycardia (220)***. Glycopyrrolate was discontinued and restarted 3 days later (0.3 mg IV every 6 hours); the same reaction occurred. Glycopyrrolate was discontinued after three doses and he recovered after an unspecified amount of time. The patient was an "ex 28 wkr" with chronic lung disease and was hospitalized and intubated for ruling out aspiration pneumonia when the events occurred.

ISR 3894292, US (2002): An 18-year-old male received glycopyrrolate 1 mg daily by mouth for 28 days to treat hyperhidrosis. Three days after discontinuing glycopyrrolate, he went to the emergency room (ER) where work up showed ***low blood oxygen and "very dry tissues, burned tissues"***; he was treated with oxygen and assisted respiration. No other medications were detected in his system. He spent one week in the hospital. On an unspecified date, he experienced a ***pneumothorax and emphysema***. Follow-up from the mother ~5 weeks after being discharged stated that he was still experiencing ***shortness of breath, high pulse (110/min), and low blood oxygen***. Two days later, the mother reported that the blood tests, heart rate, and X-rays showed improvement.

ISR 4495805*, US (1983): A 16-year-old female received one dose of glycopyrrolate 0.5 mg IV while undergoing surgery for mandibular retrognathia. She also received diazepam, cefazolin, dexamethasone, topical phenylephrine, topical lidocaine, propofol, lidocaine, fentanyl, vecuronium, lidocaine with epinephrine (at the surgical site), isofluorane, nitrous oxide, and oxygen. Ten minutes after the procedure started, she experienced ***persistent hypertension*** that was treated with esmolol (blood pressure 200/100, preoperative was 115/65) and ***sinus tachycardia (150***, preoperative was 67). Approximately 10 minutes later, a pink frothy exudate was noted in her endotracheal tube and a chest radiograph revealed ***fulminant pulmonary edema***. An EKG showed global ***elevation in all ST segments and sinus tachycardia***. Over the next 30 minutes, her hemodynamic instability resolved (blood pressure=110-135/70, heart rate=90-110) and she was treated with furosemide. The surgery was completed and she was transferred to the intensive care unit. A postoperative EKG indicated a ***T-wave abnormality and a prolonged QT*** and cardiac enzymes one hour postoperatively revealed a troponin level of 3.5 (normal, <0.3), indicating ***myocardial ischemia***. Her troponin level peaked 17 hours after surgery at 8.3. An echocardiogram the next day showed a ***global decrease in left ventricular contractility (hypokinesis) with an ejection fraction of 35%***. With continued diuresis, she began to improve. The pulmonary edema resolved on postoperative day 2. The wall motion abnormalities and ejection fraction resolved on postoperative day 3. She was discharged on postoperative day 4. Her medical history included hemolytic uremic syndrome when she was 3 years old, tonsillectomy, and adenoidectomy. The authors believe an idiosyncratic response to medications is the most likely etiology for the events and that the cardiopulmonary compromise cannot be explained by the actions of a single medication. *Literature citation: J Oral Maxillofac Surg 2004;62:240-3.*

ISR 5578846*, US (2007): An 18-year-old female enrolled in study Sc-GLYCO-06-01 received glycopyrrolate 12.5 mL syrup three times daily by mouth for at least 4.8 months to treat pathologic drooling. Approximately 4.6 months after starting therapy, she went to the ER after experiencing ***restlessness, discomfort, elevated white count (22,800), fever (100.4 F), O2 saturation of 92%, and tachycardia***. ***Urine cultures came back positive for enterococcus and gamma hemolytic streptococcus***; she was treated with IV fluids, hydromorphone, ondansetron, lorazepam, oxygen, levofloxacin, and placement of a NG tube and Foley catheter. She was discharged 3 days later and treatment with glycopyrrolate restarted. She had an extensive medical history that included cerebral palsy, spasticity (carnitine, baclofen), seizures (valproate, carbamazepine), quad tetraplegia, osteoporosis (alendronate), scoliosis- spinal fusion, bilateral hip replacement, recurrent streptococcal infection, vesicoureteral reflux- bilateral ureter implant, constipation (polyethylene glycol 3350, Fleet enema, bisacodyl), GERD (ranitidine, metoclopramide), sedation (clonidine), sinusitis (budesonide), pharyngitis, nasal congestion (guaifenesin), dry lips (Eucerine), tonsillectomy, adenoidectomy, strabismus, amenorrhea cramping (naproxen), weakness, poor coordination, and dantrolene therapy. *Study Sc-GLYCO-06-01 is a 6-month, open label study to assess the safety and efficacy of oral glycopyrrolate liquid for the treatment of pathologic (chronic moderate to severe) drooling in pediatric patients 3-18 years old with cerebral palsy or other neurologic conditions.*

ISR 5943546*, US (2008): A 2-year-old male received an accidental overdose of glycopyrrolate injectable (one dose of 5 mg/mL instead of 1 mg / 5 mL) given via GT to decrease salivary secretions for surgery. He began therapy with glycopyrrolate 1 mg / 5 mL three times daily on an unknown date prior to the tonsillectomy and adenoidectomy. Two days after the accidental overdose of glycopyrrolate, he experienced ***rapid heart rate (180), respiratory distress, pulmonary hypertension, urinary retention (catheter placed), and pain***. He was transferred to the PICU, placed on a ventilator, and treated with milrinone and nitroprusside. On unknown dates, he experienced ***low blood oxygen level, Pseudomonas pneumonia*** (treated with multiple unspecified antibiotics and pain medications), and ***dehydration*** (treated with unspecified intravenous fluids). He was discharged from the hospital approximately one month after the surgery, but still had complaints of ***fatigue and lung scarring*** from the pneumonia and ventilator treatment. His medical history included trisomy 21, seizures (topiramate, divalproex sodium), GERD (ranitidine), allergies (cetirizine), obstructive sleep apnea (chloral hydrate), constipation (polyethylene glycol 3350), excessive salivary secretions, and placement of a GT at 10 months of age.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

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/s/

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