

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022571Orig1s000

OTHER 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: July 26, 2010

To: Susan Walker, MD., Director
Division of Dermatology and Dental Products

Through: Kellie Taylor, PharmD, MPH, Associate Director
Division of Medication Error Prevention and Analysis

From: Lubna Najam, M.S., PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Cuvposa (Glycopyrrolate) Oral Solution, 1 mg/5 mL

Application Type/Number: NDA 022571

Applicant: Shionogi Pharma, Inc.

OSE RCM #: 2010-41

1 INTRODUCTION

This review responds to a request from the Division of Dermatology and Dental Products for a review of the revised Cuvposa labels and labeling submitted on July 23, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE RCM #2010-41 dated July 21, 2010.

2 MATERIAL REVIEWED

The Applicant provided revised label and labeling on July 23, 2010. We also evaluated the recommendations pertaining to the previous revision in OSE review #2010-41.

3 DISCUSSION

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2010-41. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

4 CONCLUSIONS AND RECOMMENDATIONS

The revised label and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time.

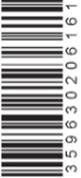
If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

5 REFERENCES

OSE Review #2010-41, Label, and Labeling Review for Cuvposa (Glycopyrrolate) Oral Solution. Najam, L: July 23, 2010

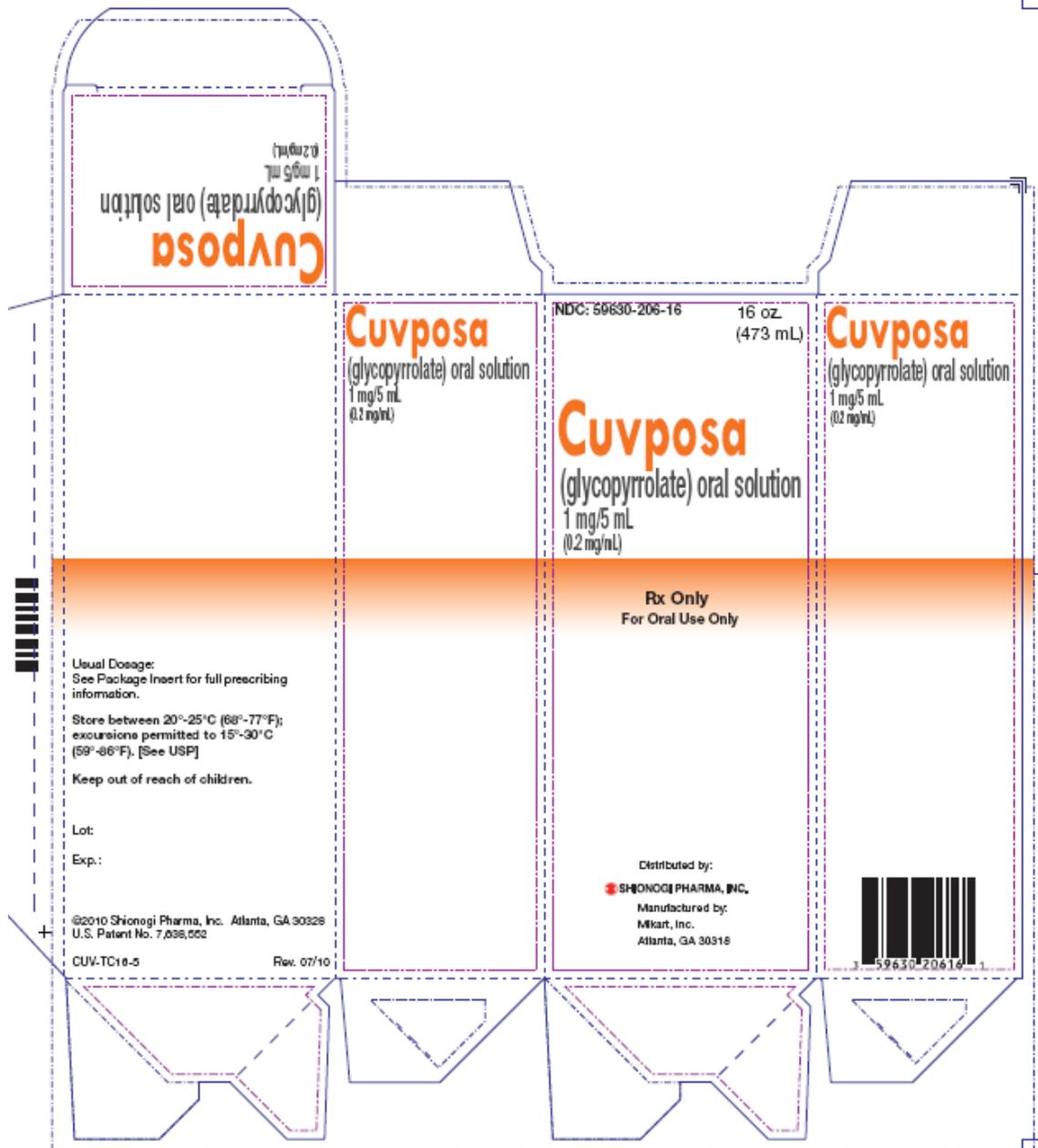
6 APPENDICES

Appendix A: Container Label

Exp: Lot:	NDC: 59630-206-16	16 oz. (473 mL)
	Cuvposa (glycopyrrolate) oral solution 1 mg/5 mL (0.2 mg/mL)	 3 59630 206161
Store between 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP]	Rx Only For Oral Use Only	Usual Dosage: See Package Insert for full prescribing information. Keep out of reach of children.
CUV-TL16-5 Rev. 07/10	Distributed by: SHIONOGI PHARMA, INC. Manufactured by: Mikart, Inc., Atlanta, GA 30318 ©2010 Shionogi Pharma, Inc. Atlanta, GA 30328.	U.S. Patent No. 7,638,552

Exp: Lot:	NDC: 59630-206-47	16 oz. (473 mL)
	Cuvposa (glycopyrrolate) oral solution 1 mg/5 mL (0.2 mg/mL)	
Store between 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP]	Rx Only For Oral Use Only PROFESSIONAL SAMPLE- NOT TO BE SOLD	Usual Dosage: See Package Insert for full prescribing information. Keep out of reach of children.
CUV-SL16-5 Rev. 07/10	Distributed by: SHIONOGI PHARMA, INC. Manufactured by: Mikart, Inc., Atlanta, GA 30318 ©2010 Shionogi Pharma, Inc. Atlanta, GA 30328.	U.S. Patent No. 7,638,552

Appendix B: Carton Labeling



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/

LUBNA NAJAM
07/28/2010

KELLIE A TAYLOR
07/28/2010



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: July 23, 2010

To: Susan Walker, MD, Division Director
Division of Dermatology and Dental Products

Through: Melina Griffis, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Lubna Najam, M.S., Pharm.D, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Cuvposa (Glycopyrrolate) Oral Solution, 1 mg/5 mL

Application Type/Number: NDA 022571

Applicant/sponsor: Shionogi Pharma, Inc.

OSE RCM #: 2010-41

1. INTRODUCTION

This review responds to a request from the Division of Dermatology and Dental Products for a review of the revised Cuvposa labels and labeling submitted on July 21, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE #2010-41 dated May 28, 2010.

2. METHODS AND MATERIALS REVIEWED

The Applicant provided revised label and labeling on July 21, 2010. We also evaluated the recommendations pertaining to the previous revision in OSE review #2010-41.

3. CONCLUSION AND RECOMMENDATIONS

Review of the revised documents show that the majority of the revisions are satisfactory with respect to DMEPA's recommendations under OSE review #2010-41, however, we still have concerns related to the prominence of the strength presentation. We provide recommendations below and request they be communicated to the Applicant prior to approval.

3.1 COMMENTS TO THE APPLICANT

Container Labels (trade and sample)

- 1 Add parenthesis around the secondary strength expression of 0.2 mg/mL.
- 2 Relocate both strength expressions to the left under the established name.
- 3 To accommodate for the relocation of the strength expression, relocate the Rx Only and For Oral Use only statements below the orange line

Carton Labeling

- 1 Add parenthesis around the secondary strength expression of 0.2 mg/mL.
- 2 Relocate both strength expressions to the left under the established name.

If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Janet Anderson at 301-796-0675.

4. REFERENCES

*OSE Review #2010-41, Label, and Labeling Review for Glycopyrrolate Oral Solution.
Najam L: May 28, 2010*

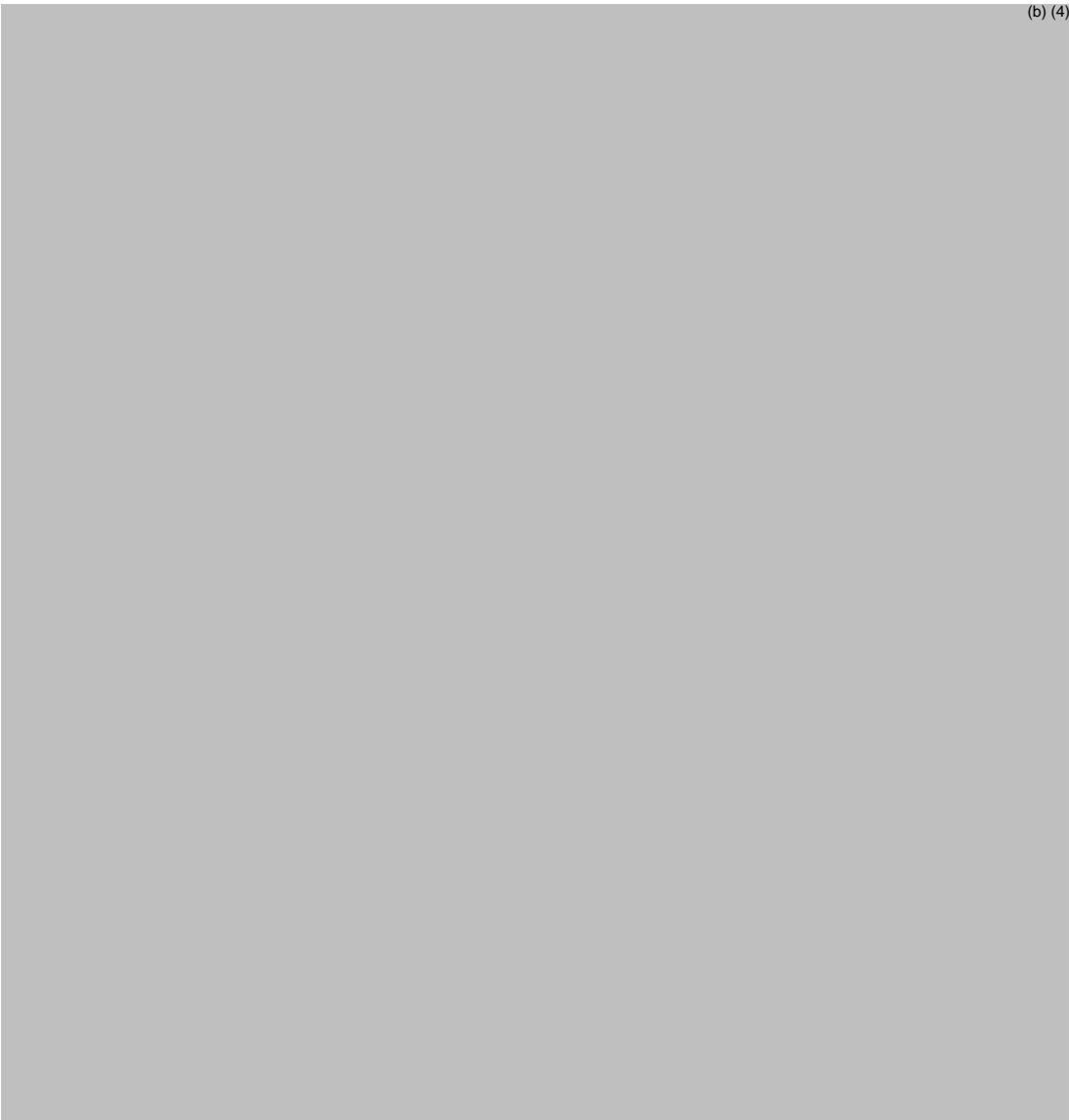
APPENDICES



(b) (4)

Appendix C: Carton Labeling

(b) (4)



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/

LUBNA NAJAM
07/23/2010

MELINA N GRIFFIS
07/23/2010

DENISE P TOYER
07/23/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 22, 2010

From: Yichun Sun, Ph.D.
Review Chemist,
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 22-571

Subject: Recommendation for Approval

After the CMC review dated June 29, 2010 was written, the applicant updated the container and carton labels for the NDA on July 22, 2010.

The updated container labels are reviewed according to 21 CFR 201 and found acceptable (see the review of the labels presented below).

This updated information does not affect the previous "Approval" recommendation stated in the memorandum dated July 13, 2010.

CMC related information provided for the container and carton labels:

Bottle Label

(b) (4)



As shown in the above mock-up bottle label, the following items are provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net contents**
- **“Rx only”**
- **Storage conditions**
- **Bar code**
- **Lot number and expiration date**
- **NDC number**
- **Name of manufacturer/distributor**
- **“See package insert for full prescribing information”**

Evaluation: Acceptable. The mock-up bottle label provides all the required information as per 21 CFR 201.

Carton Label

(b) (4)



As shown in the above mock-up carton label, the following items are provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net quantity of dosage form**
- **“Rx only”**
- **Lot number and expiration date**
- **Storage conditions**
- **Bar code**
- **NDC number**
- **Name of manufacturer/distributor**
- **“See package insert for full prescribing information”**

Evaluation: Acceptable. The mock-up carton label provides all the required information as per 21 CFR 201.

Physician Sample Label (bottle)



As shown in the above physician sample label, the following items are provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net contents**
- **“Rx only”**
- **Storage conditions**
- **Lot number and expiration date**
- **NDC number**
- **Name of manufacturer/distributor**
- **“See package insert for full prescribing information”**

Note: The bar code requirement does not apply to prescription drug samples according to 21 CFR 201.25 (Bar code label requirements). No carton will be used for the physician sample.

Evaluation: Acceptable. The physician sample label provides all the required information as per 21 CFR 201.

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/

YICHUN SUN
07/22/2010

MOO JHONG RHEE
07/22/2010
Chief, Branch IV

MEMORANDUM

To: Dawn Williams, RN, BSN, USPHS
Division of Dermatology and Dental Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: July 6, 2010

Re: Comments on draft labeling for [TRADENAME] glycopyrrolate oral solution
NDA 22-571

We have reviewed the proposed label for [TRADENAME] (glycopyrrolate) oral solution (FDA versions dated 5/14/10 and 6/25/10 and received by SEALD on 5/21/10 and 6/25/10, respectively) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

19 pages have been withheld in full immediately following this page as B4
(Draft Labeling).

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/

IRIS P MASUCCI
08/03/2010

LAURIE B BURKE
08/03/2010



**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: June 4, 2010

To: Susan Walker, M.D., Director
Division of Dermatology and Dental Products (DDDP)

Through: Mary Willy, PhD, Deputy Director
Division of Risk Management (DRISK)

LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): [TRADENAME] (glycopyrrolate) Oral Solution

Application Type/Number: NDA 22-571

Applicant/sponsor: Shionogi Pharma, Inc.

OSE RCM #: 2010-448

1 INTRODUCTION

Shionogi Pharma, Inc. submitted an original 505 (b) (2) New Drug Application, NDA 22-571, on September 25, 2009 for [TRADENAME] (glycopyrrolate) Oral Solution. The proposed indication for [TRADENAME] (glycopyrrolate) Oral Solution is for the treatment of (b) (4) (chronic (b) (4) severe) drooling in patients aged 3 to 16 years with cerebral palsy, (b) (4) or other neurologic conditions associated with problem drooling. The Reference Listed Drugs for this product include:

- Robinul (glycopyrrolate) Injection 0.2 mg/mL. via cross reference to NFA 17-558, sponsored by Baxter Healthcare
- Robinul (glycopyrrolate) Injection 0.2 mg/mL , via cross reference to NDA 14-764, sponsored by A.H. Robins
- Robinul and Robinul Forte (glycopyrrolate) tablets 1 mg and 2 mg, NDA 12-827, held by Sciele Pharma Inc.

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for [Tradename] (glycopyrrolate) Oral Solution. Please let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft [TRADENAME] (glycopyrrolate) Oral Solution Prescribing Information (PI) submitted on September 25, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on May 14, 2010.
- Draft [TRADENAME] (glycopyrrolate) Oral Solution Patient Package Insert (PPI) submitted on September 25, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on May 14, 2010.
- Draft [TRADENAME] (glycopyrrolate) Oral Solution Caregiver Manual, submitted on April 2, 2010.

3 DISCUSSION

The Applicant submitted an Amendment to their NDA on April 2, 2010, proposing a Caregiver Manual for review as labeling. This Caregiver Manual represents a revised booklet based on a Training Manual that was developed by the Applicant at the request of the Agency, for use in the clinical trials with the product. We note that the Training manual focused on detailed instructions to Caregivers for titration of the product, as well as information for recognizing and managing side effects. The Caregiver Manual proposed in the April 2, 2010 submission, (b) (4)

(b) (4) does not include information about dose titration; it instead provides detailed information about side effects of TRADENAME and what to do. FDA-approved patient labeling may include Patient Package Inserts, Instructions for Use, and Medication Guides. The proposed Booklet for Parents and Caregiver does not fit into any of these patient labeling categories.

4 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

DRISK did not review the proposed Booklet for Parents and Caregivers because it is not a part of patient labeling. We recommend that DDDP advise the Applicant that if they wish to provide this information to parents and caregivers, that it should be submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for review as a direct-to-consumer piece.

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.



Please let us know if you have any questions.

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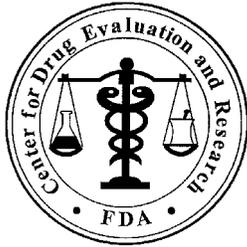
Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

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/s/

SHARON R MILLS
06/04/2010

MARY E WILLY
06/04/2010
I concur



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: May 28, 2010

To: Susan Walker, MD, Division Director
Division of Dermatology and Dental Products

Through: Melina Griffis, RPh, Team Leader
Kellie Taylor, PharmD, MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Lubna Najam, M.S., Pharm.D, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Glycopyrrolate Oral Solution, 1 mg/5 mL

Application Type/Number: NDA 022571

Applicant/sponsor: Sciele Pharma, Inc.

OSE RCM #: 2010-41

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1. INTRODUCTION

This review summarizes DMEPA's evaluation of the proposed labels and labeling for Glycopyrrolate Oral Solution (NDA 022571) for areas of vulnerabilities that could lead to medication errors. DMEPA evaluated the proposed proprietary name, (b) (4) for this product and concluded that it was unacceptable. The applicant submitted an alternate name, Cuvposa, which is being evaluated under a separate review (OSE # 2010-927).

2. METHODS AND MATERIALS REVIEWED

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The Division of Medication Error Prevention and Analysis (DMEPA) conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors that describe the risks associated with Glycopyrrolate that could negatively impact the safe use of the oral solution. An AERS search was conducted on May 17, 2010 using the tradename "Robinul", active ingredients "Glycopyrrolate" and verbatim term "Glycopyrro%" and "Robinul%". The search was limited to the following routes: nasal, oral, Sublingual

The reports were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the reports to determine if the error could be applicable to the oral product and thus pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors involving concomitant drugs, or different dosage form) were excluded from further analysis. Duplicate reports were combined into cases. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA),¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, carton and insert labeling. This review focuses on the labels and labeling submitted as part of the September 28, 2009 original NDA submission. See Appendices A-C for images of the proposed container labels and carton labeling.

3. RESULTS

3.1 AERS RESULTS

The FDA Adverse Event Reporting System (AERS) search retrieved a total of 60 cases. Fifty seven (57) of these cases were excluded from further analysis because these cases described adverse events, adverse events related to concomitant medications or product quality issues. The remaining three (n=3) cases were identified as relevant to this review and are described below. These cases all involved off label use of Glycopyrrolate.

One case (ISR 1437646-9) identified a 13-month-old child receiving the injection formulation orally. The patient received the medication for about two months and experienced loss of appetite.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The second case (ISR 5943546-7) involved a 27-month-old patient receiving Glycopyrrolate injection via his gastrostomy (GI) tube. In addition the case also involved the patient being administered a dose of 5 mg/mL instead of the prescribed dose of 1 mg/5mL. The patient experienced tachycardia, pulmonary hypertension, urinary retention, and pain. The patient was admitted to the ICU and placed on ventilator.

The third case (ISR 1763235-2) reported an infant receiving Glycopyrrolate tablets crushed and formulated in a suspension. The patient experienced “untoward side effects.” No other information was available in this report.

4. DISCUSSION

Our search of the FDA AERS retrieved cases of wrong route administration error. We identified two cases where the injection formulation was given via the oral route and one case in which Glycopyrrolate tablets were compounded into a suspension. In one of these cases the off label use resulted in overdose. The introduction of an oral formulation should alleviate some of this misuse of the injection and tablet formulation and hopefully reduce the risk of error associated with off label use.

We note that the oral formulation currently uses the strength expression of “1 mg/5 mL.” Since the product dosing is weight based (mg/kg) and prescribed doses will vary and may not correspond to the standard 5 mL or a teaspoon as usually seen with oral liquid products. We considered 0.2 mg/mL as an alternative expression of strength for ease of dose calculation and product administration as typically products that are dosed based on weight use a X mg/mL expression. We determined that the 0.2 mg/mL strength expression would not be ideal for this product for the following reason.

Glycopyrrolate is currently available as a 0.2 mg/mL injection formulation, which is identical in concentration to the proposed oral formulation (1 mg/5 mL or 0.2 mg/mL). As noted above we have identified cases in AERS involving off label use of the injection solution administered orally. With the availability of the oral solution, it is conceivable that both the injection and oral solution may be stored in the same area and may also be listed alphabetically in pharmacy computer systems and in computerized physician order entry systems. An overlap in the primary expression of strength (0.2 mg/mL) between the oral solution and injection formulations could increase the risk of prescribing and selection error and may lead to wrong route and wrong drug administration errors. Conversely, using an alternate expression of strength such as 1 mg/5 mL for the oral solution may help health care practitioners to distinguish the two dosage forms. However, for ease of dosage calculation in pediatric patients, we would recommend adding a secondary expression of strength to the oral solution noting the concentration per mL (0.2 mg/mL) below the 1 mg/5 mL. We also recommend the addition of the statement “For Oral Use Only” to avoid any potential confusion with the injection formulation.

In addition, our evaluation of the labels and labeling also identified several areas of needed improvement to increase the prominence of information and provide clarity. The labels require increased prominence of the established name and product strength. We address these in our recommendations in Section 5 below.

5. CONCLUSION AND RECOMMENDATIONS

Due to the off label use of the injection formulation via the oral route and similarity in the concentration between the injection and oral liquid formulation, we do anticipate medication errors related to the confusion between these two dosage forms. Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize risks of off label use with these products. We provided recommendations to the insert labeling in Section 3.1

Comments to the Division for discussion during the labeling meetings. Section 3.2 Comments to the Applicant contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Janet Anderson at 301-796-0675

5.1 COMMENTS TO THE DIVISION:

A. FULL PRESCRIBING INFORMATION

1. CLINICAL PHARMACOLOGY- Section 12

The pharmacokinetics section (12.3) uses the abbreviation I.V to represent intravenous Glycopyrrolate. The abbreviation, I.V can be misinterpreted to mean I.U or I.N. As part of a national campaign² to decrease the use of dangerous abbreviations, FDA agreed to not use such abbreviations in the approved labeling of products. Therefore we recommend that IV be replaced with the text “intravenous”.

2. HOW SUPPLIED/STORAGE AND HANDLING- (Section 16)

The following information is provided on the container label, (b) (4)

We recommend that the storage statement be consistent throughout the label and labeling.

B. PATIENT INFORMATION

The following information is provided on the container label, (b) (4)

We recommend that the storage statement be consistent throughout the label and labeling.

5.2 COMMENTS TO THE APPLICANT:

A. Container Label (1 mg/5 mL; 16 oz. retail and sample container)

1. We note the established name is ½ the size of the proprietary name, but it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). In addition, the gray font used in the presentation of the established name makes it difficult to read. We recommend the font color of the established name be changed to a more prominent color that is easier to read.
2. Increase the prominence of the product strength statement by increasing the font size and color to be commensurate with the proprietary name.
3. The prominence of the net quantity statement on the principal display panel may distract from other important information. Revise the label to decrease the prominence of the net quantity statement by using non bold lettering and removing the colored band highlighting

² ISMP and FDA Campaign to Eliminate Use of Error-Prone Abbreviations available at <http://www.ismp.org/tools/abbreviations/>

the net quantity. In addition relocate the statement to a less prominent section of the label away from the product strength.

4. Revise the presentations of the strengths and volumes by adding a space between the number and the unit of measure (i.e., 1 mg/5 mL rather than 1mg/5 mL).
5. For ease of dosage calculation in pediatric patients, we recommend adding a secondary expression of strength 0.2 mg/mL below the 1 mg/5 mL. The secondary strength expression should have decreased prominence than the 1 mg/5 mL expression.
6. In accordance to 21 CFR 201.25, provide a barcode on the container label.
7. Revise the statement, [REDACTED] (b) (4) to read “Usual Dosage: See package insert for full prescribing information.”
8. Since Glycopyrrolate is also available in an Injection formulation, to avoid any potential confusion, add a statement “For Oral Use Only” below the “RX Only” statement.
9. The size of the company logo and distributor information is more prominent than the strength and established name. Decrease the size of the company logo and distributor information.
10. Separate the statement “Store between ...” and the statement [REDACTED] (b) (4) by using bold letters or space in between to increase the prominence of the [REDACTED] (b) (4) statement.

B Carton Labeling (1 mg/5 mL 16 oz. container)

1. See comments A1- A8
2. In accordance with 21 CFR 201.17, ensure the carton label to incorporate the expiration date and lot number.

APPENDICES

Appendix A: Container Label



Appendix B : Container label-sample pack

(b) (4)



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/

MELINA N GRIFFIS
05/28/2010

KELLIE A TAYLOR
05/28/2010

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
05/28/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA 022571	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: TRADENAME Established/Proper Name: Glycopyrrolate Dosage Form: Oral Solution Strengths: 1 mg/mL		
Applicant: Shionogi Pharma, Inc. Agent for Applicant (if applicable):		
Date of Application: September 25, 2009 Date of Receipt: September 28, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: July 28, 2010	Action Goal Date (if different): Target date July 14, 2010	
Filing Date: November 27, 2009	Date of Filing Meeting: October 27, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 3- New Dosage Form		
Proposed indication(s)/Proposed change(s): treatment for (b) (4) (chronic, (b) (4) severe) drooling in pediatric patients aged 3-16 with cerebral palsy, (b) (4), or other neurologic conditions associated with problem drooling		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)	

Other:	<input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 61,716				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			Orphan Designation
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?			X	Granted Orphan Designation- User Fee exempt
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:			X		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>			X		Applicant requested 7-year exclusivity due to Orphan Designation.

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?	X			
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>		X		

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	Electronic Submission

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>			X	PREA does not apply- Orphan Designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			IRT/QT Consult- sent 2/3/2010 SEALD Consult- sent 2/3/2010 DRISK Consult- sent 1/29/2010 DEPI Consult- sent 1/27/2010 DMEPA Consult- sent 1/27/2010 DDMAC Consult- sent 1/27/2010 DPV Consult- sent 3/9/2010

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 27, 2009

NDA #: 022571

PROPRIETARY NAME: TRADENAME

ESTABLISHED/PROPER NAME: glycopyrrolate

DOSAGE FORM/STRENGTH: Oral solution, 1 mg/mL

APPLICANT: Shionogi Pharma, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND: This is a liquid formulation intended to be titrated for the appropriate dose. It was granted Orphan Designation on June 9, 2006 for ages 3-16 years of age for treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients with neurologic disorders. They have chosen a 505(b)(2) regulatory pathway and are relying on the Agency's finding of safety and efficacy for the listed drug Robinul (glycopyrrolate) Injection, 0.2mg/mL.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dawn Williams	Y
	CPMS/TL:	Barbara Gould	N
Cross-Discipline Team Leader (CDTL)	Jake Kelsey		Y
Clinical	Reviewer:	Fred Hyman	Y
	TL:	Jake Kelsey	Y

Clinical Pharmacology	Reviewer:	Dennis Bashaw	Y
	TL:	Dennis Bashaw	Y
Biostatistics	Reviewer:	Kathy Fritsch	Y
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Norm See	Y
	TL:	Barbara Hill	Y
Product Quality (CMC)	Reviewer:	Yichun Sun	N
	TL:	Shulin Ding	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues: Need to clarify what the basis of the 505(b)(2) is. It is unclear on what they are relying. Will advise them in the 74-Day letter that they don't qualify for a 505(b)(2), and they must be a 505(b)(1).</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p><input type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: Inspections at this time won't be practical due to the length of time that has passed since the clinical studies were completed.</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>

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<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

Comments:	
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<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Susan Walker, M.D., F.A.A.D., Division Director	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAWN WILLIAMS
05/21/2010

BARBARA J GOULD
05/27/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: April 14, 2010

To: Dawn Williams, DDDP
Fred Hyman, DDS, DDDP
Jake Kelsey, DDS, DDDP

From: Andrew Haffer, PharmD,

Re: NDA# 22-571
Glycopyrrolate Oral Solution, 1 mg/5 mL

DDMAC has reviewed the draft PI and PPI labeling for Glycopyrrolate Oral Solution, 1 mg/5 mL. DDMAC's comments are based on the proposed draft labeling in the eRoom titled "NDA 022571, glycopyrrolate label, 3/23/10.doc.url."

DDMAC's comments are provided directly in the PDF document attached (see below).

If you have any questions about DDMAC's comments on the PI please contact Andy Haffer. For questions on DDMAC's comments on the PPI please contact Shefali Doshi.

12 Pages of Draft Labeling has been withheld immediately following this page as B4 (CCI/TS)

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/

ANDREW S HAFFER
04/14/2010

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER 2010-011
APPLICATION NUMBER NDA 022571
LETTER DATE September 2, 2009
DATE OF CONSULT REQUEST February 2, 2010
DUE DATE April 5, 2010

REVIEW DIVISION DDDP
CLINICAL REVIEWER Fred Hyman
REVIEW DIVISION PM Dawn Williams

SEALD REVIEWER Elektra J. Papadopoulos
REVIEW COMPLETION DATE April 14, 2010

DRUG NAME Glycopyrrolate Oral Solution
APPLICANT Shionogi Pharma, Inc.

ENDPOINT CONCEPTS/ INSTRUMENTS (1) Drooling as measured by the mTDS;
(2) Prospective safety assessment as measured by the mBMRS
(3) Global rating scales (caregiver/parent and investigator)

INDICATION Treatment of (b) (4) (chronic (b) (4) severe) drooling

INTENDED POPULATION Pediatric patients ages 3-16 years
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STUDY ENDPOINT REVIEW

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products regarding NDA 022571 for the use of Glycopyrrolate Oral Solution (glycopyrrolate) for (b) (4) (chronic (b) (4) severe) drooling in pediatric patients ages 3-16 years. The patient population comprises children with cerebral palsy (b) (4) or any other neurologic condition associated with (b) (4) severe drooling.

Glycopyrrolate is an anticholinergic drug initially approved in 1961. The drug may be associated with several common anticholinergic adverse effects including (but not limited to) constipation, urinary retention, flushing and increased heart rate. During clinical development, study drug dosing was to be based on the patient's weight and subsequently increased every 5–7 days using a dose titration schedule until the desired reduction in drooling is reached, undesirable side effects become limiting, or the highest dose in the titration schedule was reached, whichever occurred first.

Prospective safety assessments by caregivers as well as investigators were included in phase 3. During clinical development, the “Caregiver’s Manual” an educational tool was used in order to assist caregivers in recognizing the common anticholinergic adverse effects. One of the study objectives was to evaluate the utility of the Caregiver Manual in educating caregivers. However, no outcomes related to the safety or efficacy of the study drug were recorded or reported as a part of the Caregiver’s Manual, and this tool is not reviewed in this SEALD endpoints review.

The SEALD review provides comment on the following measurement tools used in phase 3:

- (1) Modified 9-point Teacher’s Drooling Scale (mTDS) a caregiver-rating scale used as the primary efficacy measure;
- (2) Modified Behavioral and Medical Rating Scale (mBMRS), a caregiver rating scale intended for prospective safety assessment; and
- (3) Global assessments by investigators and parents/caregivers to evaluate the statement “This is a worthwhile treatment.”

This review concludes the following:

- (1) The mTDS scale might be a content valid tool to support labeling claims and was agreed upon with the Agency prior to the 2006 publication of the draft PRO Guidance for Industry. A PRO dossier has not been provided for Agency review, however. Reference and description of this scale should be minimized in product labeling.
- (2) The mBMRS scale does not appear to have been developed according to the standards of the PRO guidance for industry. The mBMRS includes several items that are proxy-reported. The

STUDY ENDPOINT REVIEW

Agency discourages the use of proxy-reported outcomes. (b) (4)

(3) The global assessments by investigators and parents/caregivers to evaluate the statement “This is a worthwhile treatment” are NOT content valid. (b) (4)

(4) Study 2 was a non-randomized, open-label study. (b) (4)

(5) The documents found within the case report forms (see appendices of this review) are not the actual diary that was sent home with the caregivers. These documents are presumably representative of the caregiver-reported diary that included the mTDS and mBMRS, but are not the actual copy of the diary. It appears that the investigator completed the CRF based on review of the parent/caregiver diary. Preferably, a copy of the actual instrument should be provided to NDA for Agency review. Additionally, the script that was used for the investigator interview version of the mBMRS used as Visits 4, 5, 6 and 7 was not found within the NDA submission.

2 ENDPOINT REVIEW

It is important to be familiar with the following definitions and concepts described in the final PRO Guidance for Industry published in December 2009.

Patient-reported outcome (PRO) — A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient’s response.

Proxy-reported outcome — A measurement based on a report by someone other than the patient reporting as if he or she is the patient. A proxy-reported outcome is not a PRO. A proxy report also is different from an observer report where the observer (e.g., clinician or caregiver), in addition to reporting his or her observation, may interpret or give an opinion based on the observation. We discourage use of proxy-reported outcome measures particularly for symptoms that can be known only by the patient.

The Agency discourages proxy-reported outcome measures for patient populations who are cognitively impaired or unable to communicate. For patients who cannot respond for themselves (e.g., cognitively impaired), we encourage observer reports that include only those events or behaviors that can be **observed**. As an example, observers cannot validly report an infant’s pain intensity (a sensation) but can report infant behavior thought to be caused by pain (e.g., crying).

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2.1 Instruments

Modified 9-point Teacher's Drooling Scale (mTDS):

The primary efficacy assessment used a caregiver assessment, the mTDS. The mTDS is a 9-point scale used to assess the degree of drooling. To this reviewer's knowledge, SEALD has not previously reviewed this scale.

mTDS assessments were to be performed by the parent/caregiver at baseline (on two days within 7 days before randomization) and on days 7, 14, and 21, and 28.

A representation of the mTDS is found in Appendix A.

Modified Behavioral and Medical Rating Scale (mBMRS):

The mBMRS is another caregiver-assessment/instrument used as part of a prospective safety assessment and was used to assess medication-associated adverse events.

The mBMRS was to be administered by the parent/caregiver three times weekly, every two to three days, during the overall eight-week trial as part of the parent/caregiver diary. The investigator was also to administer the mBMRS as a scripted verbal questionnaire at Visits 4, 5, 6 and 7.

Comment: The script for this verbal questionnaire was not found within the NDA submission.

A representation of the mBMRS is found in Appendix B.

Global Assessments (Caregivers and Investigators):

The global assessments by investigators and parents/caregivers to evaluate the statement "This is a worthwhile treatment" can be found in Appendix C. The global assessments were to be completed once, at Week 8 (completion of therapy).

2.2 Claim Structure

The following (small font) appears in the sponsor's proposed draft package insert.

(b) (4)



STUDY ENDPOINT REVIEW

(b) (4)



STUDY ENDPOINT REVIEW

Comments: As stated earlier in this review, the global assessments by investigators and parents/caregivers to evaluate the statement “This is a worthwhile treatment” are NOT content valid. (b) (4)

(b) (4)

Comments: As stated earlier in this review, Study 2 was a non-randomized, open-label study. (b) (4)

2.3 Endpoint Model

The trial endpoints are as follows.

Primary Efficacy Endpoint: Change from baseline to Week 8 evaluations of the modified TDS as administered by the parent/caregivers.

Secondary Efficacy Endpoints:

Caregiver’s, Patient’s and Physician’s Global Assessments were designated as secondary study endpoints.

Safety: The mBMRS data was to be summarized descriptively. Adverse events (AEs) were to be tabulated overall. AEs identified by mBMRS were to be listed versus those AEs identified by other means.

2.4 Conceptual Framework

The measurement concept of the mTDS scale is “drooling” and the tool seemingly intends to combine concepts of both drooling frequency as well as severity within a single item as shown below.

The measurement concept of the mBMRS is “medication-associated adverse events”. The item stems of this tool are shown below. Each item has the following response options: 1 = Not at all; 2 = Just a little; 3 = Quite a bit; and 4 = Very much.

mBMRS Item Stems

Restless, overactive
Excitable, impulsive
Disturbs other children
Fails to finish things he starts, short attention span
Constantly fidgeting
Inattentive, easily distracted
Demands must be met immediately, easily frustrated
Cries often and easily
Mood changes quickly and drastically
Temper outbursts, explosive and unpredictable behavior
Overly serious, sad or sensitive
Change in coordination and/or body control
Fearful
Diarrhea / Constipation (circle one and score)
Drowsy
Nasal congestion
Vomiting
Irritable
Dry mouth
Difficulty urinating
Flushing of the skin on the face or body
Headache
Blurred vision
Heart palpitations
Increased heart rate
Skin rash
Skin hives

Comments:

As stated earlier in this review, the Agency discourages the use of proxy reporting, whereby a person other than the patient reports on symptoms or feelings as if he/she were the patient. The mBMRS includes several such items as including the following: fearful; drowsy; headache; blurred vision; and heart palpitations. These items describe symptoms or sensations that cannot be observed directly.

Items such as “increased heart rate” are not appropriate for a parent/caregiver assessment. It is unclear whether the caregiver training on measurement of the actual heart rate was adequate. Further it is unclear what “increased” is rated (e.g., relative to baseline or other).

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The questionnaire includes items that include more than one concept in a single item (e.g., overly serious, sad or sensitive).

2.5 Content Validity

Information on instrument development has not been provided for any of these instruments.

Modified 9-point Teacher's Drooling Scale (mTDS):

The mTDS is a single item scale that combines the concept of frequency and severity of drooling. The sponsor has not provided information to describe the development of the scale. Because the scale is administered by caregivers, qualitative research with caregivers of patients would be a part of the empiric evidence supportive of content validity. No mention of such studies was found in the NDA submission.

mBMRS:

The mBMRS includes several such items as including the following: fearful; drowsy; headache; blurred vision; and heart palpitations. These items describe symptoms or sensations that cannot be observed directly. As stated earlier in this review, the Agency discourages the use of proxy reporting, whereby a person other than the patient reports on symptoms or feelings as if he/she were the patient.

Items such as “increased heart rate” do not appear appropriate for a parent/caregiver assessment. It is unclear whether the caregiver training on measurement of the actual heart rate was adequate. Further it is unclear what “increased” is rated (e.g., relative to baseline or other).

The questionnaire includes items that include more than one concept in a single item (e.g., overly serious, sad or sensitive). This is generally discouraged.

Global Assessments (Caregivers and Investigators):

These scales are not content valid because it is unclear what criteria investigators and caregivers are using to make these assessments. Further, the term “worthwhile” does not describe a well-defined effect of treatment. Therefore, these tools cannot be considered well-defined and reliable for use as a key study endpoint (b) (4)

2.6 Other Measurement Properties

A description of other measurement properties such as test-retest reliability, construct validity and ability to detect change was not provided. Importantly, however, the scale has demonstrated ability to detect change in the randomized, placebo-controlled phase 3 clinical study and to show a difference between treatment groups (active-placebo).

2.7 Interpretation of Scores

mTDS: A responder was defined as any patient with at least a 3-point improvement from baseline in mTDS assessment at the 2, 4, 6 and 8-week visits. For example, an mTDS value of 7 at baseline had to improve to a value of ≤ 4 ($7 - 3 = 4$) during treatment for the patient to be designated a responder.

2.8 Language Translation and Cultural Adaptation

Not applicable.

2.9 Study Protocol

Protocol: FH-00-01

Title: A Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Oral Glycopyrrolate Liquid (1 mg per 5 mL) for the Management of Problem Drooling Associated with Cerebral Palsy or other Neurologic Conditions in Children

This was a multi-center, randomized, double-blind, placebo-controlled study that was 8 weeks in duration. Thirty-six male or female patients (ages 3 through 16 years) with cerebral palsy, mental retardation, or any other neurologic condition associated with problem drooling were randomized in a 1:1 manner to receive glycopyrrolate liquid or placebo. Doses of study medication were titrated over a 4-week period.

Investigators were to encourage performance of all assessments by the same parent/caregiver throughout the study.

Study assessments are summarized in the following table. The following instructions were found in the foot notes to this table.

Parent/caregiver mTDS assessments. The mTDS assessments should be made on non-school days when the parent/caregiver can observe the patient during the entire course of the day. For school children, assessments should be made on non-school days (weekend or holiday). Each mTDS assessment will cover a 30-60 minute time period to evaluate both severity and frequency of drooling.

STUDY ENDPOINT REVIEW

	Visit 1		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Screen (Day -21 to -9)	Baseline (Day -8 to 0)	Day +1	Week 2 (Day 14)	Week 4 (Day 28)	Week 6 (Day 42)	Week 8 (Day 56)	Dropout
Informed Consent	X							
Inclusion/ Exclusion	X							
Demographics	X							
Medical History	X							
Physical Exam	X (r)						X (r)	X (r)
Randomization			X					
Study Medication			X (n)	X (i)	X (i)	X	X	X
Caregiver Training	X (k)		X (k)				X (k)	X (k)
Blood Chemistry	X (a)						X (a)	X (a)
CBC	X (b)						X (b)	X (b)
Urinalysis	X (s)						X(s)	X (s)
12-Lead ECG	X (q)						X (q)	X (q)
Pregnancy Test	X						X	X
mTDS Caregiver	X (d,e) Dispense Diary			X (d,f)	X (d,f)	X (d,f)	X (d,f)	X (d,f, t)
Global Assessments							X (j)	X (j)
mBMRS	X (m) Instruct Caregiver (k), Dispense Diary		X (l)	X (l)	X (l)	X (l)	X (m)	X (m)
Caregiver Diary (c)	X, Instruct & Dispense		X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X
Concomitant Meds	X		X	X	X	X	X	X

Study endpoints are described in Section 2.3 of this review (Endpoint Model).

The parents/caregivers were not to discontinue the medication on their own volition. The parent/caregiver, after having received training via the Caregiver's Manual to identify adverse glycopyrrolate effects, could however, decrease the dose level due to concerns about AEs.

In the case of such a dose decrease, the parents/caregivers were to inform the investigator as soon as possible.

Teachers and school nurses were not to change the dose level or skip a dose of the medication, except in the event of reasonable safety or AE concern, in which case, they were required to inform the parent/caregiver as soon as possible.

Appendix A

mTDS

The 9-point mTDS scale is:

- 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, tray and objects become wet; **occasionally**
- 9 = Profuse: clothing, hands, tray and objects become wet; **frequently**

STUDY ENDPOINT REVIEW

Appendix B

Modified Behavioral and Medical Rating Scale (mBMRS):

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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/

ELEKTRA J PAPADOPOULOS
04/14/2010

LAURIE B BURKE
04/14/2010

**DCRP/Interdisciplinary Review Team for QT Studies Consultation:
ECG Study Review**

NDA	22571
Brand Name	ROBINUL®
Generic Name	Glycopyrrolate Oral Solution
Sponsor	Shionogi Pharma
Indication	(b) (4) (chronic (b) (4) severe) drooling in pediatric patients
Dosage Form	Oral Solution
Drug Class	Anticholinergic
Therapeutic Dosing Regimen	(b) (4) doses range from approximately 0.01 to about 0.1 mg/kg three times daily. The maximum recommended dosage is 0.1 mg/kg three times daily.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Maximum tested dose in Phase 3 clinical trials-the maximum daily dose reported for any given patient was 0.266 mg/kg in FH-00-01 and 0.308 mg/kg in Sc- GLYCO-06-01
Submission Number and Date	SDN 001, September 28, 2009
Clinical Division	DDDP/HFD 540

1 RESPONSES TO QUESTION POSED BY REVIEW DIVISION

Please review this study report for comment on the sponsor’s above stated conclusion. Specifically, does DCRP agree that the data do not suggest a further need for monitoring through a PMC or PMR? Please also review the following sections of the proposed PI pertaining to cardiac events: 1) Section 4, Contraindications; 2) Section 5.5 General Anticholinergic Effects; and 3) Table 1: Adverse events, which includes “Heart Rate Increased.”

DCRP/QT-IRT RESPONSE

DDDP has requested that we address two issues 1) QT assessment for glycopyrrolate and 2) Effects of glycopyrrolate related to tachycardia/tachyarrhythmias

QT Assessment for Glycopyrrolate

- While there are limitations in studies FH-00-01 and Sc-GLYCO-06-01 because of sparse ECG collection and absence of time matched PK sampling, the data along with the post-marketing experience suggest that large effects on the QT or other ECG intervals are unlikely.
- Exposure (Cmax and AUC data) with multiple dosing of glycopyrrolate is unavailable. The clinical pharmacology review for the NDA is still pending. If the review team concludes that, since exposures in the pediatric population with

multiple dosing of the oral solution is similar to or lower than with the approved products a TQT study would not be required. On the contrary if higher exposures is expected or if the population PK analysis is inconclusive, it may be reasonable to have the sponsor conduct a TQT study as a post-marketing commitment.

Effects of glycopyrrolate related to tachycardia/tachyarrhythmia's

- Consistent with its anticholinergic properties, glycopyrrolate increased the heart rate in the placebo controlled study (FH-00-01) by 10.5 bpm and had a variable effect in ScGLYCO-06-01. While there was a significant number of tachycardic outliers, only two subjects in FH-00-01 (compared to 1 in placebo group) had tachycardia reported as an AE and one subject 1403 in Sc-GLYCO-06-01 had a supra-ventricular arrhythmia but the case was confounded because of co-morbidities (chronic respiratory failure, UTI with sepsis) and concomitant medications.
- Compared to adults, children (except those with underlying heart disease or right heart failure secondary to chronic aspiration) are likely more tolerant of this HR increase since they have higher heart rates at baseline compared to adults and this seems consistent with the MGPS data mining analysis results of fewer events in the pediatric age group (see section 4.1.3). However, we defer to the OSE opinion for incidence of symptomatic cardiac arrhythmias and tachycardia with off-label use in this population.
- The sponsor has not proposed any labeling related to ECG effects. Unstable cardiovascular status is listed under contraindications. Tachyarrhythmias and tachycardia are listed under general anticholinergic effects (warning and precautions) and in the adverse reactions (clinical trials and post-marketing experience) section. We do not have any additional comments in this regard; the proposed labeling seems reasonable.

2 BACKGROUND

2.1 MARKET APPROVAL STATUS

Glycopyrrolate (glycopyrrolate bromide) is a synthetic quaternary ammonium antimuscarinic, structurally related to atropine. Glycopyrrolate tablets (Robinul and Robinul Forte Tablets) have been FDA-approved since 1961 for the adjunctive treatment of peptic ulcer disease in adults, and Robinul Injection has been FDA-approved since 1975 as preoperative or intraoperative medication in adults and children 2 years of age (5 µg/kg iv, maximum dose of 0.1 mg) and older to reduce salivary, tracheobronchial, and pharyngeal secretions. This New Drug Application [505(b)(2)] is filed in support of a new oral solution dosage form for glycopyrrolate (Robinul) to treat pathologic chronic drooling in children with mental retardation. Off-label use of crushed tablets in pediatric patients for the same indication is frequent according to the sponsor. DPPP has consulted OSE regarding incidence of tachycardia related AEs, related to off-label use in this population.

2.2 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary eCTD 2.6.2

Studies per the S-7B guidelines (hERG channel and in-vivo ECG effects) were not performed. The sponsor reports increases in heart rate in rat, rabbits and anesthetized dogs.

2.3 PREVIOUS CLINICAL EXPERIENCE

The overall glycopyrrolate oral solution program consists of two pivotal Phase 3 studies and a Phase 1 clinical pharmacology study. The safety data summarized in this SCS were obtained from 175 pediatric (≥ 3 years old to ≤ 18 years old) patients with chronic moderate to severe drooling associated with cerebral palsy or other neurologic conditions.

Sponsor's post-marketing data review (Source: Summary of Clinical Safety, eCTD 2.7.4)

“A comprehensive literature search was conducted to obtain information pertaining to the possible risk of QT/QTc prolongation or Torsades de Pointes with glycopyrrolate administration. The public scientific literature was searched for articles that discuss the clinical effects of glycopyrrolate on the heart; specifically those relating to QTc and adverse effects including cardiac rhythm. In addition, a list of drugs known to prolong the QT interval is located at <http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm#>. This website was searched to determine whether glycopyrrolate is listed among those drugs known to be associated with Torsades de Pointes.

“Results of the literature search and website review revealed that anticholinergic agents can cause a multitude of cardiac effects. There were two publications that suggested glycopyrrolate and atropine can cause prolongation of QTc. However, after having been on the US market for 48 years, there is no evidence from this literature search or on the referenced QT websites that glycopyrrolate is associated with a risk of Torsades de Pointes.

“Furthermore, glycopyrrolate information that is available from the literature addressing QTc prolongation was obtained in settings where confounding variables can be implicated (extubation and concomitant medications). No published clinical reports were identified involving Torsades de Pointes or QT prolongation for oral glycopyrrolate. This information suggests that oral glycopyrrolate solution is unlikely to be associated with QTc cardiac safety concerns.”

From the PI in the Adverse Reactions section for glycopyrrolate injection:

A large rectangular area of the document is redacted with a solid grey fill. In the top right corner of this redacted area, the text "(b) (4)" is printed in a small font.

[REDACTED] (b) (4)

2.4 CLINICAL PHARMACOLOGY

From the PI for glycopyrrolate injection:

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

3 SPONSOR'S SUBMISSION

OVERVIEW

A retrospective cardiac safety analysis for both Phase 3 studies (FH-00-01, Sc-GLYCO-06-01) was performed [REDACTED] (b) (4) For both studies, ECGs were retrospectively sent to a core ECG laboratory for a treatment-blinded measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

3.1.1 Study FH-00-01

3.1.2 Title

A Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Oral Glycopyrrolate Liquid (1 mg per 5 mL) for the Management of Problem Drooling Associated with Cerebral Palsy or Other Neurologic Conditions in Children

3.1.3 Protocol Number

FH-00-01

3.1.4 Study Dates

07 Nov 2002 to 03 April 2007

3.1.5 Objectives

- To determine the efficacy of oral glycopyrrolate liquid (1 mg per 5 mL) for the management of problem drooling in children with cerebral palsy or other neurologic conditions;
- To assess the safety of glycopyrrolate liquid in this patient population;
- To assess the effectiveness of the Training Manual: “Glycopyrrolate Liquid for the Treatment of Problem Drooling Associated with Cerebral Palsy or Other Neurologic Conditions in Children; For Parents and Caregivers of Patients and to educate parents/caregivers about drooling; and
- To identify the common adverse effects and beneficial effects of glycopyrrolate liquid in cerebral palsy patients or patients with other neurologic conditions suffering from drooling.

3.1.6 Study Description

This was a multi-center, randomized, double-blind, placebo-controlled, balanced, parallel, eight-week study. Thirty-six male or female patients (ages 3 through 16 years) with cerebral palsy, mental retardation, or any other neurologic condition associated with problem drooling were randomized in a 1:1 manner to receive glycopyrrolate liquid or placebo.

3.1.7 Treatment Regimen

Doses of study medication were titrated over a 4-week period to optimal response beginning at 0.02 mg/kg three times a day (TID) up to 0.1 mg/kg TID or to a total maximum dose of 3 mg TID or Dose Level 5, whichever was lesser, as indicated in the Dose Titration Schedule.

Table 1: Dose Titration Schedule

Glycopyrrolate Liquid (1 mg/5 mL)											
Doses described were given three times daily.											
Weight		Dose Level 1		Dose Level 2		Dose Level 3		Dose Level 4		Dose Level 5	
Kg	lb	(~0.02 mg/kg)		(~0.04 mg/kg)		(~0.06 mg/kg)		(~0.08 mg/kg)		(~0.1 mg/kg)	
13-17	27-38	0.3 mg	1.5 mL	0.6 mg	3 mL	0.9 mg	4.5 mL	1.2 mg	6 mL	1.5 mg	7.5 mL
18-22	39-49	0.4 mg	2 mL	0.8 mg	4 mL	1.2 mg	6 mL	1.6 mg	8 mL	2.0 mg	10 mL
23-27	50-60	0.5 mg	2.5 mL	1.0 mg	5 mL	1.5 mg	7.5 mL	2.0 mg	10 mL	2.5 mg	12.5 mL
28-32	61-71	0.6 mg	3 mL	1.2 mg	6 mL	1.8 mg	9 mL	2.4 mg	12 mL	3.0 mg	15 mL
33-37	72-82	0.7 mg	3.5 mL	1.4 mg	7 mL	2.1 mg	10.5 mL	2.8 mg	14 mL	3.0 mg	15 mL
38-42	83-93	0.8 mg	4 mL	1.6 mg	8 mL	2.4 mg	12 mL	3.0 mg	15 mL	3.0 mg	15 mL
43-47	94-104	0.9 mg	4.5 mL	1.8 mg	9 mL	2.7 mg	13.5 mL	3.0 mg	15 mL	3.0 mg	15 mL
>48	>105	1.0 mg	5 mL	2.0 mg	10 mL	3.0 mg	15 mL	3.0 mg	15 mL	3.0 mg	15 mL

Starting Dose: The initial starting dose for all patients was always Dose Level 1. Every five to seven days the dose was titrated up one dose level until the optimal dose was attained.

Maximum Dose: No patient was dosed more than 3 mg (15 mL) three times daily (TID) or at Dose Level 5 TID, whichever was the lesser dose for the patient's weight category.

3.1.8 ECG Collection

12-lead ECGs were obtained at the site using site recorders at Screening and then at the end of the study on Day 56 or whenever a patient dropped out of the trial. The ECGs were then retrospectively sent to a core ECG laboratory for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

Original copies of the paper ECGs were digitally scanned and interval duration measurements were obtained by semi-automated methods.

The ECG analysis was conducted in Lead II and when Lead II was not analyzable then the analysis was conducted in Lead V5, followed by the most appropriate lead. ECG readers were blinded to subject identifiers, treatment and visit.

3.1.9 Sponsor's Results

The ECG analysis was performed on all randomized subjects with at least one available baseline and on treatment ECG.

3.1.9.1 Study Subjects

38 patients were randomized to treatment in the study. The cardiac related exclusion was: Patients who have medical conditions contraindicating anticholinergic therapy including cardiac arrhythmias or tachycardia, or clinically significant ECG abnormalities as determined by the investigator.

Five patients discontinued the study prematurely. Patient 6009 in the glycopyrrolate group and Patient 1002 in the placebo group discontinued due to AEs. Patient 4004 in the glycopyrrolate group and Patient 8001 in the placebo group discontinued because of patient/parent decision, and Patient 6003 in the placebo group discontinued because of lack of efficacy.

3.1.9.2 Statistical Analyses

The results as mean change from baseline and new outliers from baseline are shown below.

Table 4-1	All glycopyrrolate	Placebo
Total N [some parameters with less sample size by 1-2 subjects]	20	17
Heart Rate in bpm *	+4.2	-6.3
Heart Rate tachycardic outliers N (%)	3 (16%)	0
Heart Rate bradycardic outliers N (%)	0	0
PR in ms *	+1.5	+1.2
PR outliers N (%)	0	0
QRS in ms *	+0.5	-0.1
QRS outliers N (%)	0	0
QT in ms *	-8.3	+1.0
QT new >500 ms N (%)	0	0
QTcF in ms *	-0.4	-2.5
QTcF new >500 ms N (%)	0	0
QTcF new >480 ms N (%)	0	0
QTcF 30-60 ms inc N (%)	0	1 (6%)
QTcF >60 ms inc N(%)	0	0
QTcB in ms *	+4.6	-5.9
QTcB new >500 ms N(%)	0	0
QTcB new >480 ms N (%)	0	0
QTcB 30-60 ms inc N (%)	1 (6%)	0
QTcB >60 ms inc N (%)	0	0
New abnormal U waves N (%)	0	0
New ST segment depression changes N (%)	0	0
New T wave inverted N (%)	0	0
New 2 nd and 3 rd Degree Heart Block, Complete RBBB & LBBB, MI N (%)	0	0

bpm = beats per minute; ms=milliseconds, QTcB: Bazett correction, QTcF= Fridericia correction; RBBB=right bundle branch block; LBBB= left bundle branch block, MI= myocardial infarction; N="new" means not present at baseline and only seen after baseline * Mean change from baseline.

Source Table 4-1, cardiac safety report for FH-00-01

The mean change from baseline and placebo for heart rate in bpm was +10.5, a clinically relevant increase. There were 16% new tachycardic outliers (> 100 bpm and 25% change from baseline) on glycopyrrolate compared to none on placebo.

No new ECG morphologic changes were of clinical significance were identified in this trial.

3.1.9.3 Safety Analysis

- There were no deaths in this study.
- Five patients in the study, all of whom were in the glycopyrrolate group, experienced a total of seven severe AEs. Most of these events affected the GI system.
- One patient (Patient 8002) in the glycopyrrolate group with history of spastic quadriparesis, history of prematurity complicated by intraventricular hemorrhage and resultant symptomatic generalized epilepsy experienced a serious adverse event (SAE) of generalized tonic-clonic seizure activity followed by generalized convulsive activity (b) (4) after taking his last dose of study medication.
- One patient in each treatment group had the study drug permanently discontinued due to an AE (abdominal distension and aggravated constipation/ dry mouth).

- Seventeen (46%) children were reported to experience side effects while taking glycopyrrolate. The most common side effects were dry mouth and/or thick secretions (19%), urinary retention (19%), flushing (11%). Constipation, pseudo-obstruction, agitation and personality changes were also reported.
- Only reported ECG abnormality was sinus tachycardia. Two subjects had “heart rate increased reported as AE with glycopyrrolate compared to one subject in the placebo group.

3.2 STUDY Sc-GLYCO-06-01

3.2.1 Title

A six month, multicenter, 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 to 18 years of age with cerebral palsy and other neurologic conditions

3.2.2 Protocol Number

Sc-GLYCO-06-01

3.2.3 Study dates

April 3, 2007- May 30, 2008

3.2.4 Objectives

The specific objectives of the Sc-GLYCO-06-01 study were:

- To assess the safety of oral glycopyrrolate liquid given chronically to pediatric patients ages 3 through 18 years with chronic, moderate to severe, drooling associated with cerebral palsy or other neurologic conditions, and
- To evaluate the continued efficacy of Glycopyrrolate Liquid for the management of chronic, moderate to severe, drooling in this patient population.

3.2.5 Study Description

This was a 24-week, multi-center, open-label design to assess the safety and efficacy of oral glycopyrrolate liquid (1 mg per 5 mL) for the management of chronic, moderate to severe, drooling associated with cerebral palsy or other neurologic conditions in children.

3.2.6 Treatment Regimen

The dose titration schedule is outlined below:

Glycopyrrolate Liquid (1 mg/5mL)

Doses described below are to be given three times daily.

Weight		Dose Level 1		Dose Level 2		Dose Level 3		Dose Level 4		Dose Level 5	
kg	lb	(~0.02 mg/kg)		(~0.04 mg/kg)		(~0.06 mg/kg)		(~0.08 mg/kg)		(~0.1 mg/kg)	
13-17	27-38	0.3 mg	1.5 ml	0.6 mg	3 ml	0.9 mg	4.5 ml	1.2 mg	6 ml	1.5 mg	7.5 ml
18-22	39-49	0.4 mg	2 ml	0.8 mg	4 ml	1.2 mg	6 ml	1.6 mg	8 ml	2.0 mg	10 ml
23-27	50-60	0.5 mg	2.5 ml	1.0 mg	5 ml	1.5 mg	7.5 ml	2.0 mg	10 ml	2.5 mg	12.5 ml
28-32	61-71	0.6 mg	3 ml	1.2 mg	6 ml	1.8 mg	9 ml	2.4 mg	12 ml	3.0 mg	15 ml
33-37	72-82	0.7 mg	3.5 ml	1.4 mg	7 ml	2.1 mg	10.5 ml	2.8 mg	14 ml	3.0 mg	15 ml
38-42	83-93	0.8 mg	4 ml	1.6 mg	8 ml	2.4 mg	12 ml	3.0 mg	15 ml	3.0 mg	15 ml
43-47	94-104	0.9 mg	4.5 ml	1.8 mg	9 ml	2.7 mg	13.5 ml	3.0 mg	15 ml	3.0 mg	15 ml
≥48	≥105	1.0 mg	5 ml	2.0 mg	10 ml	3.0 mg	15 ml	3.0 mg	15 ml	3.0 mg	15 ml

Starting Dose: The starting dose for all patients is always Dose Level 1. Then, every 5-7 days, titrate up one Dose Level only until the optimal dose is attained.

Maximum Dose: No patient is to be dosed higher than 3 mg (15 mL) three times daily or Dose Level 5 three times daily, whichever is the lesser dose for the patient's weight category.

3.2.7 ECG Collection

12-lead ECGs were obtained at the site using site recorders at screening and at the end of titration at Week 4 and then at Weeks 12 and 24. The ECGs were then retrospectively sent to a core ECG laboratory following the same procedures as outlined in section 3.1.8.

3.2.8 PK assessments

The population pharmacokinetic variables of glycopyrrolate were to be assessed by measurement of plasma glycopyrrolate concentrations pre-dose and at 4 time points post dose (i.e., 30 minutes, 1 hour, 2 hours, and 4 hours post-dose).

Once dose titration was completed (Visit 3) and the optimal dose for the patient was determined, the patient was scheduled for his/her pharmacokinetic blood sample collection visits. One pre-dose sample and 4 post-dose samples were to be collected over 4 visits. Sample collection could be performed at any 4 out of the 5 scheduled visits following dose titration (Visits 3 to 7 or Weeks 4, 8, 12, 16, and 20).

Reviewer's Comments: ECG and PK assessments were not time-matched.

3.2.9 Sponsor's Results

The ECG analysis was performed on all randomized subjects with at least one available baseline and on treatment ECG.

3.2.9.1 Study Subjects

Male or female patients, ages 3 through 18 years, with cerebral palsy, mental retardation or any other neurologic condition associated with chronic, moderate to severe, drooling as outlined in the inclusion/exclusion criteria were to be enrolled in the study. The cardiac related exclusion was similar to FH-00-01. The maximum dose level for the ITT population was as shown below

Table 11-2 Maximum Dose Level: Intent-to-Treat Population

Dose Range (TID)	Maximum Dose N=137	Last Dose N=137
> 0 mg/kg to < 0.02 mg/kg	5 (3.7%)	11 (8.0%)
≥ 0.02 mg/kg to < 0.04 mg/kg	14 (10.2%)	27 (19.7%)
≥ 0.04 mg/kg to < 0.06 mg/kg	44 (32.1%)	44 (32.1%)
≥ 0.06 mg/kg to < 0.08 mg/kg	39 (28.5%)	32 (23.4%)
≥ 0.08 mg/kg to < 0.1 mg/kg	25 (18.2%)	18 (13.1%)
≥ 0.1 mg/kg	10 (7.3%)	5 (3.7%)

Source: Appendix 16.2, Listings 16.2.9.1 through 16.2.9.3, and 16.2.14

Source: Table: 11-2, CSR for Sc-GLYCO-06-01

Of the 160 patients enrolled in this study, 137 received at least one dose of study drug and were included in the ITT population. Of the 137 patients who received study drug, 103 (75.2%) completed the study, and 34 (26.3%) discontinued from the study early. Nineteen patients stopped treatment with glycopyrrolate liquid because of an AE. These 19 patients included 3 patients who had an AE with a fatal outcome, 2 patients who withdrew consent to participate in the study (patient/parent decision), and 14 patients who terminated participation in the study because of an AE.

3.2.9.2 Statistical Analyses

The results as mean change from baseline and new outliers from baseline are shown in the following table.

Table 4-1 Time-Averaged Analysis of All Patients							
	Treatment Group						All Patients
	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Dose Level 5	Dose Level 6	
	0 ≤ .02	.02 ≤ .04	.04 ≤ .06	.06 ≤ .08	.08 ≤ .1,	or ≥ .1	
Total N [some parameters with less sample size by 1-2 subjects]	4	24	38	34	17	5	125
Heart Rate in bpm *							
Heart Rate tachycardic outliers N (%)	1 (25%)	6 (26%)	7 (19%)	6 (18%)	1 (6%)	0	21 (17%)
Heart Rate bradycardic outliers N (%)	0	0	1 (3%)	0	0	0	1 (1%)
PR in ms *	-0.5	0.5	1.9	3.7	0.0	4.2	1.9
PR outliers N (%)	0	0	1 (3%)	0	0	0	1 (1%)
QRS in ms *	1.3	3.0	1.0	0.3	2.6	2.0	1.5
QRS outliers N (%)	0	0	0	0	0	0	0
QT in ms *	-13.3	-0.4	0.9	-7.2	11.6	2.4	0.7
QT new >500 ms N (%)	0	0	0	0	0	0	0
QTcF in ms *	-6.0	0.3	0.8	-5.7	8.1	-4.4	0.2
QTcF new >500 ms N (%)	0	0	0	0	0	0	0
QTcF new >480 ms N (%)	0	0	0	0	0	0	0
QTcF 30-60 ms inc N (%)	0	2 (9%)	1 (3%)	0	0	0	3 (2%)
QTcF >60 ms inc N (%)	0	0	0	0	1 (6%)	0	2 (2%)
QTcB in ms *	-1.5	1.2	0.6	-5.1	6.0	-8.8	-0.2
QTcB new >500 ms N (%)	0	0	0	0	0	0	0
QTcB new >480 ms N (%)	0	0	0	0	0	0	0
QTcB 30-60 ms inc N (%)	1 (25%)	2 (9%)	3 (8%)	3 (9%)	1 (6%)	0	10 (8%)
QTcB >60 ms inc N (%)	0	1 (5%)	0	0	1 (6%)	0	3 (2%)
New abnormal U waves N (%)	0	0	0	0	0	0	0
New ST segment depression changes N (%)	0	0	0	0	0	0	0
New T wave inverted N (%)	0	0	0	2 (6%)	1 (6%)	0	3 (2%)
New 2nd and 3rd Degree Heart Block, Complete RBBB & LBBB, MI N (%)	0	0	0	0	0	0	0

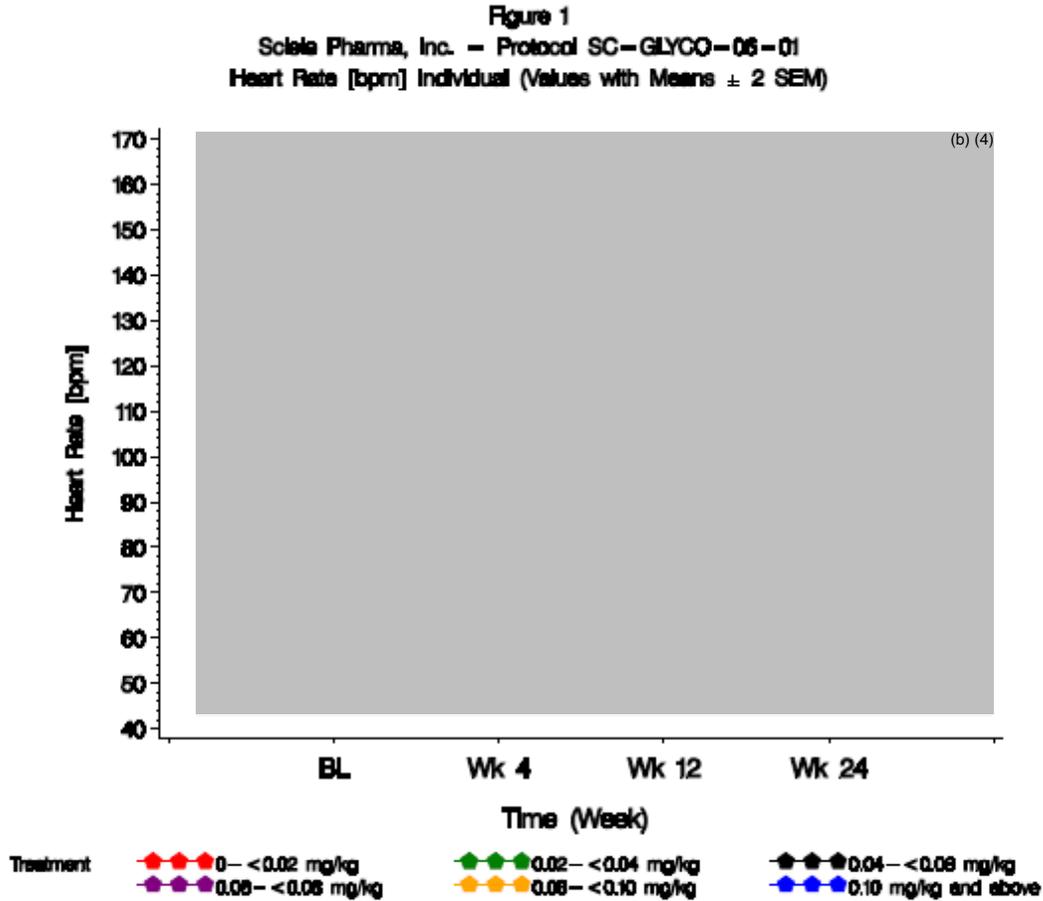
bpm = beats per minute; ms=milliseconds; QTcB: Bazett correction; QTcF= Fridericia correction; RBBB=right bundle branch block; LBBB= left bundle branch block, MI= myocardial infarction; N= "new" which means not present at baseline and only seen after baseline. * Mean change from baseline.

Source: Table 4-1 , ECG report-ScGLYCO-06-01

Reviewer's comments: other than tachycardic outliers, no other clinically relevant findings are noted.

Heart rate effects:

Unlike study FH-00-01, there was marked variability with the mean heart rate effect in this study. Across the 6 dose levels of glycopyrrolate, the mean change from baseline showed a -4 to +7 bpm change with the overall effect for all doses being a -1 bpm change. There was an overall 17% prevalence of tachycardic outliers and one bradycardic outlier at dose level 3. Only one subject had tachycardia/supraventricular arrhythmia reported as an AE.



Source: Figure 4-1, ECG report-ScGLYCO-06-01.

3.2.9.3 Safety Analysis

Although no deaths were reported for study participants while patients were treated with study drug, 3 patients died in Study Sc-GLYCO-06-01 within 30 days of the last dose of study drug. Patient 1403 died of multi-organ failure, (b) (4) after the last dose of study drug, Patient 1709 died of aspiration pneumonia, (b) (4) after the last dose of study drug, and Patient 2906 died of anoxic encephalopathy, (b) (4) after the last dose of study drug.

Fourteen patients had 20 non-cardiac SAEs during the study.

The most commonly reported TEAEs 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%).

One patient (1403) in Study Sc-GLYCO-06-01 had abnormal and clinically significant ECG results at Visit 3 (Week 4). The clinically significant ECG findings were sinus tachycardia/supraventricular arrhythmia, incomplete right bundle branch block, and left atrial enlargement. This patient died of multi-organ failure before completing the study.

Eleven subjects experienced a TEAE of convulsion. One subject was discontinued secondary to the same. Patient 2603, a 5-year-old male, with grade 3 seizures for the last 15 months; seizure disorder and diagnosed at an age of 9 months, received the first dose of glycopyrrolate liquid (2 mL=0.02 mg/kg) on 26 September 2007. Concomitant medication included salbutamol, macrogol, diazepam, phenobarbital, and topiramate. On (b) (4), the patient suffered from worsening seizures that led to permanent discontinuation of study drug (last dose on 08 October 2007). In the investigator's opinion, the event of convulsion was probably related to treatment with glycopyrrolate liquid.

4 REVIEWERS' ASSESSMENT

4.1.1 Safety Assessments in the clinical trials

There are no reports of AEs related to QT prolongation including sudden death, syncope, and significant ventricular arrhythmia in the clinical trials. Subjects in both trials experienced seizures/convulsions, but these seem more likely related to underlying neurological condition of possible exacerbation because of anticholinergic effect than to repolarization effects of glycopyrrolate.

As discussed earlier, tachycardic outliers were noted in both trials. Two subjects in FH-00-01 (compared to 1 placebo) had tachycardia reported as an AE and one subject 1403 in Sc-GLYCO-06-01 had a supra-ventricular arrhythmia but the case was confounded due to co-morbidities (chronic respiratory failure, UTI with sepsis) and concomitant medications.

4.1.2 ECG Assessments

Waveforms were not submitted to the ECG warehouse for review. Based on the sponsor's analysis glycopyrrolate did not show any clear effect on heart rate. There were no significant effects on atrio-ventricular conduction, as measured by the PR interval, or depolarization, as measured by the QRS duration. The QTcF data did not show evidence of any clinically relevant changes in QTcF duration or waveform morphology. No imbalance in specific or nonspecific outliers. While there are limitations in these studies due to sparse ECG collection and absence of time matched PK sampling, the data suggest that large effects on the QT or other ECG intervals by glycopyrrolate are unlikely.

4.1.3 MGPS data mining analysis

We conducted an MGPS data mining analysis of the AERS data base (see 5.1) for AEs related to QT prolongation and other cardiac arrhythmias with glycopyrrolate using MedDRA PT's linked to HLTs "Ventricular arrhythmias and cardiac arrest, "cardiac conduction disorders, "rate and rhythm disorders" and "supraventricular arrhythmias". PTs related to QT prolongation were also included (syncope, convulsion, electrocardiogram QT prolonged). Consistent with its anticholinergic effects, the signal scores (EBGM values) were greater than 2 for several of these PTs. The lower confidence limit (EB05) was greater than 2 for ventricular extrasystoles, second degree AV block, bradycardia, tachycardia and cardiac arrest suggesting higher incidence than the background rate. However several of the case narratives had incomplete information and were often associated with co-administration of neo-stigmine in the operative setting. The EBGM values for QT prolongation and TdP were less than 2. When broken down by age groups (see 5.1.2) few events were noted in the 12-16 and 17-20 subgroups (sinus tachycardia and sinus bradycardia) with EBO5 values < 2. However, these data alone are not confirmatory and we suggest that DDDP obtains input from OSE in this matter.

5 APPENDIX

5.1 MGPS TABLES

5.1.1 Complete run (all ages)

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 2520

Dimension: 2 **Selection Criteria:** Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT

(...) **Where:** EBGm > 2.0

12 rows Sorted by Generic name, EBGm desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Glycopyrronium	Ventricular extrasystoles	Ventricular arrhythmias and cardiac arrest	9	15.3	5.00	31.3
Glycopyrronium	Atrioventricular block second degree	Cardiac conduction disorders	4	11.7	2.05	58.8
Glycopyrronium	Bradycardia	Rate and rhythm disorders NEC	21	9.36	5.64	15.2
Glycopyrronium	Tachycardia	Rate and rhythm disorders NEC	39	7.92	5.85	10.8
Glycopyrronium	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	18	4.79	3.20	6.98
Glycopyrronium	Sinus tachycardia	Supraventricular arrhythmias	4	3.82	1.50	14.6
Glycopyrronium	Ventricular tachycardia	Ventricular arrhythmias and cardiac arrest	6	3.82	1.89	7.38
Glycopyrronium	Ventricular fibrillation	Ventricular arrhythmias and cardiac arrest	5	3.34	1.56	6.59
Glycopyrronium	Arrhythmia	Rate and rhythm disorders NEC	6	2.79	1.41	5.09
Glycopyrronium	Atrioventricular block complete	Cardiac conduction disorders	3	2.66	1.01	6.15
Glycopyrronium	Atrioventricular block first degree	Cardiac conduction disorders	2	2.04	0.654	5.24
Glycopyrronium And Neostigmine	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	2	2.59	0.725	19.9

ID:	2520
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	03/11/2010 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2
Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates	Yes

correction:	
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	(b) (4)
Created on:	03/20/2010 09:07:01 EDT
User:	Suchitra Balakrishnan
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 03/11/2010 00:00:00 loaded on 2010-03-17 12:34:04.0

Dimension: 2 Selection Criteria: Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT (Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradyarrhythmia, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardiac flutter, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Chronotropic incompetence, Conduction disorder, Electromechanical dissociation, Extrasystoles, Foetal arrhythmia, Foetal heart rate deceleration, Foetal heart rate disorder, Heart alternation, Heart block congenital, Long QT syndrome, Long QT syndrome congenital, Lown-Ganong-Levine syndrome, Neonatal tachycardia, Nodal arrhythmia, Nodal rhythm, Pacemaker complication, Pacemaker generated arrhythmia, Parasystole, Paroxysmal arrhythmia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Reperfusion arrhythmia, Rhythm idioventricular, Sick sinus syndrome, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome, Wolff-Parkinson-White syndrome congenital, Convulsion) Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Syncope) **Where:** EBGm > 2.0

```
SELECT * FROM OutputData_2520 WHERE (DIM=2 AND EBGM>2.0 AND ((P1='D' AND ITEM1 IN ('Glycopyrronium','Glycopyrronium And Neostigmine') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Adams-Stokes syndrome','Agonal rhythm','Anomalous atrioventricular excitation','Arrhythmia neonatal','Arrhythmia supraventricular','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial tachycardia','Atrioventricular block','Atrioventricular block complete','Atrioventricular block first degree','Atrioventricular block second degree','Atrioventricular conduction time shortened','Atrioventricular dissociation','Atrioventricular extrasystoles','Bifascicular block','Bradyarrhythmia','Bradycardia','Bradycardia foetal','Bradycardia neonatal','Brugada syndrome','Bundle branch block','Bundle branch block bilateral','Bundle branch block left','Bundle branch block right','Cardiac arrest','Cardiac arrest neonatal','Cardiac death','Cardiac fibrillation','Cardiac flutter','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Chronotropic incompetence','Conduction disorder','Electromechanical dissociation','Extrasystoles','Foetal arrhythmia','Foetal heart rate deceleration','Foetal heart rate disorder','Heart alternation','Heart block congenital','Long QT syndrome','Long QT syndrome congenital','Lown-Ganong-Levine syndrome','Neonatal tachycardia','Nodal arrhythmia','Nodal rhythm','Pacemaker complication','Pacemaker generated arrhythmia','Parasystole','Paroxysmal arrhythmia','Postural orthostatic tachycardia syndrome','Rebound tachycardia','Reperfusion arrhythmia','Rhythm idioventricular','Sick sinus syndrome','Sinoatrial block','Sinus arrest','Sinus arrhythmia','Sinus bradycardia','Sinus tachycardia','Sudden cardiac death','Sudden death','Supraventricular extrasystoles','Supraventricular tachyarrhythmia','Supraventricular tachycardia','Tachyarrhythmia','Tachycardia','Tachycardia foetal','Tachycardia paroxysmal','Torsade de pointes','Trifascicular block','Ventricular arrhythmia','Ventricular asystole','Ventricular extrasystoles','Ventricular fibrillation','Ventricular flutter','Ventricular pre-excitation','Ventricular tachyarrhythmia','Ventricular tachycardia','Wandering pacemaker','Withdrawal arrhythmia','Wolff-Parkinson-White syndrome','Wolff-Parkinson-White syndrome congenital','Convulsion','Electrocardiogram QT interval','Electrocardiogram QT interval abnormal','Electrocardiogram QT prolonged','Syncope')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

5.1.2 Generic by age run

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic By Age (S) **Run ID:** 2521

Dimension: 2 **Selection Criteria:** Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT (...)
Subset: 02-05 **Where:** EBGM > 2.0

Zero rows selected Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
--------------	----	-----	---	------	------	------

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic By Age (S) **Run ID:** 2521

Dimension: 2 **Selection Criteria:** Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT (...)
Subset: 06-11 **Where:** EBGM > 2.0

Zero rows selected Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
--------------	----	-----	---	------	------	------

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic By Age (S) **Run ID:** 2521

Dimension: 2 **Selection Criteria:** Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT (...)
Subset: 12-16 **Where:** EBGM > 2.0

1 rows Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Glycopyrronium	Sinus tachycardia	Supraventricular arrhythmias	2	5.33	0.886	47.6

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic By Age (S) **Run ID:** 2521

Dimension: 2 **Selection Criteria:** Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT (...)
Subset: 17-20 **Where:** EBGM > 2.0

1 rows Sorted by Generic name, EBGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Glycopyrronium	Bradycardia	Rate and rhythm disorders NEC	2	3.74	0.897	29.3

ID:	2521						
Type:	MGPS						
Name:	Generic By Age (S)						
Description:	Generic; Suspect drugs only; Subset by Age; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information information						
Project:	CBAERS Standard Runs						
Configuration:	CBAERS BestRep (S) (v2)						
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal						
As of date:	03/11/2010 00:00:00						
Item variables:	Generic name, PT						
Stratification variables:	Standard strata						
Subsets:	<table border="1"> <tr> <td>Variable:</td> <td>Age for Subsets</td> </tr> <tr> <td>Cumulative:</td> <td>No</td> </tr> <tr> <td>Labels:</td> <td>00-01, 02-05, 06-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71+, Unknown</td> </tr> </table>	Variable:	Age for Subsets	Cumulative:	No	Labels:	00-01, 02-05, 06-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71+, Unknown
Variable:	Age for Subsets						
Cumulative:	No						
Labels:	00-01, 02-05, 06-11, 12-16, 17-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71+, Unknown						
Highest dimension:	2						
Minimum count:	1						
Calculate PRR:	Yes						
Calculate ROR:	Yes						
Base counts on cases:	Yes						
Use "all drugs" comparator:	No						
Apply Yates correction:	Yes						
Stratify PRR and ROR:	No						
Fill in hierarchy values:	Yes						
Exclude single itemtypes:	Yes						
Fit separate distributions:	Yes						
Save intermediate files:	No						
Created by:	Empirica Signal Administrator						
Created on:	03/20/2010 09:07:25 EDT						
User:	Suchitra Balakrishnan						
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 03/11/2010 00:00:00 loaded on 2010-03-17 12:34:04.0						

Dimension: 2 Selection Criteria: Generic name(Glycopyrronium, Glycopyrronium And Neostigmine) + PT (Accelerated idioventricular rhythm, Accessory cardiac pathway, Adams-Stokes syndrome, Agonal rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradyarrhythmia, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiac arrest neonatal, Cardiac death, Cardiac fibrillation, Cardiac flutter, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Chronotropic incompetence, Conduction disorder, Electromechanical dissociation, Extrasystoles, Foetal arrhythmia, Foetal heart rate deceleration, Foetal heart rate disorder, Heart alternation, Heart block congenital, Long QT syndrome, Long QT syndrome congenital, Lown-Ganong-Levine syndrome, Neonatal tachycardia, Nodal arrhythmia, Nodal rhythm, Pacemaker complication, Pacemaker generated arrhythmia, Parasystole, Paroxysmal arrhythmia, Postural orthostatic tachycardia syndrome, Rebound tachycardia, Reperfusion arrhythmia, Rhythm idioventricular, Sick sinus syndrome, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular pre-excitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome, Wolff-Parkinson-White syndrome congenital, Convulsion, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged,) **Subset:** 02-05 **Where:** EBGM > 2.0

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SELECT * FROM OutputData_2521 WHERE (DIM=2 AND EBGM>2.0 AND SUBSET='02-05' AND ((P1='D' AND ITEM1 IN
('Glycopyrronium', 'Glycopyrronium And Neostigmine') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular
rhythm', 'Accessory cardiac pathway', 'Adams-Stokes syndrome', 'Agonal rhythm', 'Anomalous atrioventricular
excitation', 'Arrhythmia', 'Arrhythmia neonatal', 'Arrhythmia supraventricular', 'Atrial conduction time prolongation', 'Atrial
fibrillation', 'Atrial flutter', 'Atrial tachycardia', 'Atrioventricular block', 'Atrioventricular block complete', 'Atrioventricular
block first degree', 'Atrioventricular block second degree', 'Atrioventricular conduction time shortened', 'Atrioventricular
dissociation', 'Atrioventricular extrasystoles', 'Bifascicular block', 'Bradycardia', 'Bradycardia foetal', 'Bradycardia neonatal', 'Brugada syndrome', 'Bundle branch block', 'Bundle branch block bilateral', 'Bundle branch
block left', 'Bundle branch block right', 'Cardiac arrest', 'Cardiac arrest neonatal', 'Cardiac death', 'Cardiac
fibrillation', 'Cardiac flutter', 'Cardio-respiratory arrest', 'Cardio-respiratory arrest neonatal', 'Chronotropic
incompetence', 'Conduction disorder', 'Electromechanical dissociation', 'Extrasystoles', 'Foetal arrhythmia', 'Foetal heart
rate deceleration', 'Foetal heart rate disorder', 'Heart alternation', 'Heart block congenital', 'Long QT syndrome', 'Long QT
syndrome congenital', 'Lown-Ganong-Levine syndrome', 'Neonatal tachycardia', 'Nodal arrhythmia', 'Nodal
rhythm', 'Pacemaker complication', 'Pacemaker generated arrhythmia', 'Parasystole', 'Paroxysmal arrhythmia', 'Postural
orthostatic tachycardia syndrome', 'Rebound tachycardia', 'Reperfusion arrhythmia', 'Rhythm idioventricular', 'Sick sinus
syndrome', 'Sinoatrial block', 'Sinus arrest', 'Sinus arrhythmia', 'Sinus bradycardia', 'Sinus tachycardia', 'Sudden cardiac
death', 'Sudden death', 'Supraventricular extrasystoles', 'Supraventricular tachyarrhythmia', 'Supraventricular
tachycardia', 'Tachyarrhythmia', 'Tachycardia', 'Tachycardia foetal', 'Tachycardia paroxysmal', 'Torsade de
pointes', 'Trifascicular block', 'Ventricular arrhythmia', 'Ventricular asystole', 'Ventricular extrasystoles', 'Ventricular
fibrillation', 'Ventricular flutter', 'Ventricular pre-excitation', 'Ventricular tachyarrhythmia', 'Ventricular
tachycardia', 'Wandering pacemaker', 'Withdrawal arrhythmia', 'Wolff-Parkinson-White syndrome', 'Wolff-Parkinson-White syndrome congenital', 'Convulsion', 'Electrocardiogram QT interval', 'Electrocardiogram QT interval
abnormal', 'Electrocardiogram QT prolonged', ''))) ORDER BY ITEM1, EBGM desc

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These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

5.2 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	Glycopyrrolate oral solution is intended for pediatric use. For pediatric patients, the proposed optimal dose varies widely from patient to patient. Doses are often initiated at approximately 0.01 -0.02 mg/kg three times daily and titrated in increments of 0.02 mg/kg every 5-7 days. Most optimal doses range from approximately 0.01 to about 0.1 mg/kg three times daily. The maximum recommended dosage is 0.1 mg/kg three times daily.	
Maximum tolerated dose	In a 13-week oral gavage mouse toxicology study (Report 714003; which evaluated 30, 100, and 300 mg/kg/d doses), the MTD was between 30 and 100 mg/kg/day for males because there was no mortality at 30 mg/kg/d, and 30 mg/kg/d for females because there were 2 female mortalities at 30 mg/kg/d which were of uncertain relationship to glycopyrrolate administration. In a 13-week oral gavage Sprague-Dawley rat study (Report 714004; which evaluated 40, 120, and 360 mg/kg/d doses), the MTD was considered to be 120 mg/kg/d for both males and females, due to adverse effects on body weight and lymph node abscesses observed at 360 mg/kg/d.	
Principal adverse events	Common clinical drug-related AEs reported by approximately $\geq 2\%$ of a total of 157 patients given glycopyrrolate oral solution 0.006 mg/kg to 0.1 mg/kg three times daily for 8 to 24 weeks in two clinical trials (FH-00-01 and Sc-GLYCO-06-01) are as follows: constipation (18.5%), dry mouth (14.6%), flushing (11.5%), vomiting (4.5%), dysuria (3.8%), urinary retention (3.8%), somnolence (3.2%), urine output decreased (3.2%), diarrhea (3.2%), epistaxis (2.5%), lip dry (2.5%), and heart rate increased (1.3%). Constipation is a common dose limiting AE which is why titrated dose increases are recommended no more frequently than every 5-7 days.	
Maximum dose tested	Single Dose	Glycopyrrolate oral solution, 10 mL (1 mg/5mL), i.e., 2 mg given as a single dose, was evaluated in adult food effect BA study FH-00-02.
	Multiple Dose	In phase 3 clinical trials FH-00-01 (8-weeks) and Sc-GLYCO-06-01 (24 weeks) involving a total of 157 patients, the maximum per protocol glycopyrrolate oral solution dose level evaluated was 0.1 mg/kg three times daily. Recognizing that optimal doses varied widely among individual patients in FH-00-01 and Sc-GLYCO-06-01, the maximum daily dose reported for any given patient was 0.266 mg/kg in FH-00-01 and 0.308 mg/kg in Sc-GLYCO-06-01 (see Table 3, section 2.7.4 of the original NDA submission).
Exposures achieved at maximum tested dose	Single Dose	Exposure is greater in the fasting condition. In adult food effect BA study FH-00-02, glycopyrrolate oral solution, 10 mL (1 mg/5mL), i.e., 2 mg, given as a single oral dose in the fasting condition produced a mean C _{max} (%CV) of 0.318 (59.7%) ng/mL and an AUC _{0-inf} of 1.81 (60.2%) ng·hr/mL (see section 2.7.1, Table 1, in the original NDA submission).
	Multiple Dose	Multiple dose C _{max} and AUC data for oral glycopyrrolate are not available. With the exception of the pediatric population PK evaluation (n=36 subjects ages 3-18 years) in phase 3 trial Sc-GLYCO-06-01, multiple dose steady-state clinical pharmacokinetic studies have not been performed or published since oral glycopyrrolate was marketed in 1961. The population PK report for Sc-GLYCO-06-01 did not provide mean (%CV) C _{max} or AUC data.
Range of linear PK	The population PK report for study Sc-GLYCO-06-01 involving children administered Glycopyrrolate oral solution for 8 to 24 weeks indicate that glycopyrrolate pharmacokinetics appear to be linear within the recommended dosage range (see section 2.7.2.2.1.2 of the original NDA submission and the Sc-GLYCO-06-01 population PK report pages 5, 10 and 15.). Similarly, several clinical pharmacokinetic studies published in the literature since oral glycopyrrolate (Robinul Tablets) was first marketed in 1961 indicate that glycopyrrolate pharmacokinetics appear to be linear in the dosage range evaluated for the proposed indication (please see section 2.7.2.3.2, page 18, of the original NDA submission where a similar statement is provided).	
Accumulation at steady state	Using the 3 hour half-life and an 8 hour dosing interval, the calculated accumulation factor is 1.2. Steady-state accumulation clinical pharmacokinetic data are not available. However, since glycopyrrolate has a plasma half-life of approximately 3 hours (please see section 2.7.1, Table 1, in the	

	original NDA submission), and recognizing glycopyrrolate oral solution is proposed to be given three times daily, steady-state accumulation is anticipated to be minimal if any.	
Metabolites	Glycopyrrolate is excreted largely unchanged in the urine (Kaltiala E, et al, 1974); small amounts of glycopyrrolate are metabolized to several metabolites (Kagiwada K et al, 1974) (please see section 2.7.2.3.1 of the original NDA submission). The activity of glycopyrrolate metabolites has not been determined and to our knowledge has not been published.	
Absorption	Absolute/Relative Bioavailability	In children (n=6; 7-14 years of age) undergoing minor surgery, the absolute bioavailability (F) of oral glycopyrrolate tablets dissolved in diluted juice (compared with IV glycopyrrolate) was 3% with a range of 1.3 to 13.3% (standard deviation and %CV were not reported), which is a 10-fold range of oral bioavailability (Rautakorpi et al, 1998; see section 2.7.2.2.2.1 of the original NDA submission).
	Tmax	<ul style="list-style-type: none"> • 2.53 (0.50 – 6.00) hours, median (range) for glycopyrrolate fasting (from Glycopyrrolate oral solution adult food effect BA study FH-00-02, Listing 16.3.7, stamped page 0843 of the report). • Tmax values for glycopyrrolate metabolites have not been determined.
Distribution	Vd/F or Vd	After IV administration, glycopyrrolate has a mean volume of distribution in children ages 1 to 14 years of approximately 1.3 to 1.8 L/kg, with a range from 0.7 to 3.9 L/kg (see sections 2.7.2.2.2.1 and 2.7.2.2.2.2, and Rautakorpi et al 1998 and 1994 all in the original NDA submission). In adults ages 60-75 years the volume of distribution was 0.42 ± 0.22 L/kg (see section 2.7.2.2.2.3 and Ali-Melkkila T et al 1989 in the original NDA submission).
	% bound	Plasma protein binding studies have not been performed on glycopyrrolate and to our knowledge have not been published since the drug was first marketed in 1961.
Elimination	Route	<ul style="list-style-type: none"> • Approximately 65-80% of an intravenous glycopyrrolate dose was eliminated unchanged in urine in adults (please see sections 2.7.2.3.1 and 2.7.2.2.2.4 and Kaltiala E et al 1974 and Kirvela M et al 1993, in the original NDA submission). In adult patients who underwent surgery for cholelithiasis and were given a single IV dose of tritiated glycopyrrolate, approximately 85% of total radioactivity as excreted in urine and <5% was present in T-tube drainage of bile. In both urine and bile >80% of the radioactivity corresponded to unchanged drug (please see section 2.7.2.3.1 and Kaltiala E et al 1974, both in the original NDA submission).
	Terminal t½	<ul style="list-style-type: none"> • 3.0 (40.0%) hours, mean (%CV) (n=37 healthy adult subjects) for glycopyrrolate fasting (from Glycopyrrolate oral solution food effect BA study FH-00-02 (as described in section 2.7.1.2.1 of the original NDA submission) In children (n=6, 7-14 years of age) given a single IV dose of glycopyrrolate 0.005 mg/kg, the mean (range) t½z was 139 (73-239) minutes (Rautakorpi et al, 1998; as described in section 2.7.2.2.2.1 of the original NDA submission). • Terminal t½ values for glycopyrrolate metabolites have not been characterized and to our knowledge are not published in the literature.
	CL/F or CL	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) (see section 2.7.2.2.2.1 and Rautakorpi et al 1998, and section 2.7.2.2.2.2 and Rautakorpi et al 1994, all in the original NDA submission). In adults, IV clearance values were 0.54 ± 0.14 L/kg/hr (see section 2.7.2.2.2.3, Ali-Melkkila T et al 1989, in the original NDA submission). Recognizing oral bioavailability

		is low and highly variable, apparent oral clearance using population pharmacokinetic analysis (scaled by weight in children and adults) is 571 L/hr with 66.2% inter-individual variability (please see section 2.7.2.2.2.1.2 , and the Sc-GLYCO-06-01 Pop PK report , both in the original NDA submission).
Intrinsic factors	Age	Population pharmacokinetic analysis of oral and IV glycopyrrolate data from adults and children suggest that glycopyrrolate exposure (plasma concentration) is inversely proportional to weight, therefore dosing should be proportional to weight (doses should be weight-based) with no further adjustment due to age, gender or other covariates (please see Sc-GLYCO-06-01 Pop PK report , pages 15 and 62). The influence of age specifically on Cmax and AUC has not been evaluated.
	Sex	Population pharmacokinetic evaluation of adults and children administered IV or oral glycopyrrolate identified no effect of gender on glycopyrrolate clearance or systemic exposure (please see the Sc-GLYCO-06-01 Pop PK report pages 34, 50, 57 and 62, in the original NDA submission).
	Race	The pharmacokinetics of glycopyrrolate by race have not been characterized.
	Hepatic & Renal Impairment	Clinical pharmacokinetic studies of Glycopyrrolate oral solution in renal impairment patients or in hepatic impairment patients have not been performed. In one published trial, glycopyrrolate 4 mcg/kg was administered IV in uremic patients undergoing renal transplantation surgery. Mean AUC (10.6 mcg·h/L), mean plasma clearance (0.43 L/hr/kg) and mean 3-hour urinary excretion (0.7%) for glycopyrrolate in these uremic patients were significantly different than those of control patients (3.73 mcg·h/L, and 50%, respectively). Changes in Cmax were not reported. These results suggest that elimination of glycopyrrolate is severely impaired in patients with renal failure (please see section 2.7.2.2.2.4 and Kivvela M et al, 1993 , in the original NDA submission). There are no known published studies describing the pharmacokinetics of glycopyrrolate in patients with hepatic impairment.
Extrinsic factors	Drug interactions	<p>Drug-drug interactions studies have not been performed involving Glycopyrrolate oral solution. Since glycopyrrolate tablets were first marketed in 1961, drug interactions for this drug and other anticholinergics have been well characterized in the published literature. These reported interactions include the following (see excerpts from Drug Interaction Facts, 2010, and Drug Interactions Analysis and Management 2009 in section 5.4 of the original NDA submission). Also see section 2.7.2.3.1 of the original NDA.</p> <p><u>oral potassium chloride wax matrix tablets</u>: “Anticholinergics may facilitate gastric mucosal damage after ingestion of wax matrix potassium chloride tablets, but the clinical importance of this effect is not established.” (Drug Interactions Analysis and Management, 2009, p1070)</p> <p><u>cimetidine</u>: an anticholinergic (propantheline) reduced the bioavailability of oral ranitidine by about 20%; by inference this text listed glycopyrrolate as having a potential for such an interaction. (Drug Interaction Facts 2010, p404)</p> <p><u>digoxin</u>: an anticholinergic (propantheline) increased the bioavailability of the Orion oral digoxin formulation; plasma digoxin levels increased from 1.02 to 1.33 ng/ml in 9/13 subjects; other digoxin formulations were unaffected. By inference this text listed glycopyrrolate as having a potential for such an interaction (Drug Interaction Facts 2010, p404)</p> <p><u>levodopa</u>: anticholinergics homatropine and trihexyphenidyl increased Tmax and reduced Cmax of levodopa, though other studies refute these findings. By inference this text listed glycopyrrolate as having a potential for such an</p>

		<p>interaction (Drug Interaction Facts 2010, p1000)</p> <p><u>acetaminophen</u>: glycopyrrolate delayed oral absorption of acetaminophen; no data on influence of acetaminophen on glycopyrrolate (Drug Interaction Facts 2010, p12).</p> <p><u>amantadine</u>: possible potentiation of anticholinergic AEs when anticholinergics are given with amantadine (Drug Interaction Facts 2010, p80)</p> <p><u>atenolol</u>: an anticholinergic (propantheline) prolonged the absorption of atenolol (Drug Interaction Facts 2010, p275)</p> <p><u>cefprozil</u>: an anticholinergic (propantheline) increased mean residence time of cefprozil isomers, reduced the C_{max} 20% and delayed the T_{max} of cefprozil (Drug Interaction Facts 2010, p388)</p> <p><u>haloperidol</u>: an anticholinergic (benztropine or trihexyphenidyl) exacerbated symptoms of schizophrenia in patients when these drugs were added to the regimen. By inference this text listed glycopyrrolate as having a potential for such an interaction (Drug Interaction Facts 2010, p816)</p> <p><u>metformin</u>: an anticholinergic (propantheline pretreatment) increased metformin AUC 19% in increased the amount of metformin excreted unchanged in the urine by 26%. By inference this text listed glycopyrrolate as having a potential for such an interaction (Drug Interaction Facts 2010, p816)</p> <p><u>nitrofurantoin</u>: an anticholinergic (propantheline pretreatment) apparently increased bioavailability of nitrofurantoin as evidenced by increased nitrofurantoin excretion. By inference this text listed glycopyrrolate as having a potential for such an interaction (Drug Interaction Facts 2010, p1225)</p> <p><u>potassium chloride solid oral dosage forms</u>: “All solid oral dosage forms of potassium chloride are contraindicated in anyh patient in whom there is pharmacologi cause for arst or delay in tablet passage through the GI tract. Pharmacologic causes include anticholinergic agents...” By inference this text listed glycopyrrolate as having a potential for such an interaction (Drug Interaction Facts 2010, p1340)</p> <p><u>thiazide diuretics</u>: an anticholinergic (propantheline pretreatment) increased the T_{max} and AUC of hydrochlorothiazide. By inference this text listed glycopyrrolate as having a potential for such an interaction (Drug Interaction Facts 2010, p1737)</p>
	Food Effects	<p>A high fat meal was found to significantly effect the absorption of glycopyrrolate oral solutions (10 mLs, 1 mg/5mL; i.e., 2 mg dose), in healthy adults. Under fed high fat meal and fasting conditions, mean (±SD) C_{max} was 0.084 (± 0.081) ng/mL and 0.318 (± 0.190) ng/mL, respectively, and AUC_{0-inf} was 0.46 (± 0.13) ng-hr/mL and 1.81 (± 1.09) ng-hr/mL, respectively.</p>
Expected high clinical exposure scenario		<p>FDA asked the Sponsor to “Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.”</p> <p>Perhaps the worst case exposure scenario may be a child erroneously given the maximum recommended dose, 0.1 mg/kg three times daily, without first having had their dose gradually titrated up to optimal response.</p> <p>Because oral glycopyrrolate has a low (mean 3%) and highly variable (range 1.3 to 13%; n=6) bioavailability in children (Rautakorpie et al, 1998; see section 2.7.2.2.2.1 of the original NDA submission), if this particular worst case patient happens to have a relatively high bioavailability, for example 13%, and is consistently administered drug in the fasting condition (i.e., there is no concomitant food effect to reduce exposure), then since glycopyrrolate is pharmacokinetically linear, the resulting C_{max} and AUC would be expected to increase proportional to the oral dose resulting from the increased</p>

	<p>bioavailability, i.e., C_{max} and AUC would be expected to increase perhaps 5-fold (13% divided by 3%).</p> <p>However, it is reasonable to assume, given that this low and highly variable oral absorption (likely due to the polar nature of glycopyrrolate which is a quaternary amine) is similar in children and in adults, and that this range of bioavailability is therefore reflected in the upper 95% confidence interval for C_{max} and AUC as reported in the adult FH-00-02 food effect and BA trial.</p> <p>In the absence of pediatric C_{max} and AUC data, and assuming that similar weight-based doses for both adult and children produce similar C_{max} and AUC values (which is supported by the Sc-GLYCO-06-01 Pop PK evaluation), then the FH-00-02 adult BA study 2 mg dose (please see the cell just above) would be approximately 0.03 mg/kg for a 65 kg adult. This approximate dose produced a mean ± SD fasting adult C_{max} of 0.318 (± 0.190) ng/mL. The C_{max} upper 95% confidence interval for an adult fasting 0.03 mg/kg single dose would be approximately 0.7 ng/mL (0.318 + [2 x 0.190] = 0.698 ng/mL). Similarly the AUC_{0-inf} upper 95% confidence interval for an adult fasting 0.03 mg/kg single dose would be approximately 4.0 ng·hr/mL (1.81 + [2 x 1.09] = 3.99 ng·hr/mL).</p> <p>Linearly extrapolated using the above upper 95% confidence interval C_{max} and AUC values, a 0.1 mg/kg single oral dose for the worst case patient above would be expected to produce an approximate C_{max} of 2.3 ng/mL and an approximate AUC of 13.3 ng·hr/mL.</p> <p>Since Glycopyrrolate oral solution is proposed to be dosed three times daily, as described above in the "Accumulation at Steady-State" section above, the accumulation factor at steady state is calculated to be approximately 1.2. Therefore, assuming this worst case patient could tolerate this 0.1 mg/kg TID dose to steady-state, the worst case steady-state C_{max} might be 2.8 ng/mL (1.2 x 2.3 = 2.8) and the worst case AUC might be 16 ng·hr/mL (1.2 x 13.3 = 16).</p>
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUCHITRA M BALAKRISHNAN
04/06/2010

NORMAN L STOCKBRIDGE
04/06/2010

adequate and well controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:				identifies two studies as pivotal, though one is open label
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			The Division previously agreed that the submitted studies might support approval
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	There were no Agency commitments
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No foreign data were submitted
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Sponsor had data from one study and conducted literature review
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	X			
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			X	There were no pre-submission requests
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?			X	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Product is an Orphan Drug
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	No foreign data were submitted
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		Data are missing for 2 patients who were improperly excluded
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No additional CRFs were requested
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Sponsor may not have adequately addressed requirements of E14.
- What is this business about PMC contingent upon approval by 6/29/10?
-

Reviewing Medical Officer

Clinical Team Leader

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN V KELSEY
11/25/2009