

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022571Orig1s000**

**APPROVAL LETTER**



NDA 022571

**NDA APPROVAL**

Shionogi Pharma, Inc.  
Attention: Allison Lowry, RAC  
Director, Regulatory Affairs  
Five Concourse Parkway  
Suite 1800  
Atlanta, GA 30328

Dear Ms. Lowry:

Please refer to your New Drug Application (NDA) dated September 26, 2009, received September 28, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cuvposa (glycopyrrolate) Oral Solution, 1mg/5mL.

We acknowledge receipt of your submissions dated November 18, December 10, 29, and 31, 2009; January 21 and 22, February 18, 19 (2), and 22, March 8, 9, and 23, April 2, 21, 28 (2), and 30, May 7, 12, and 27, June 8, 22, and 23, and July 16, 20, 22, 27 and 28, 2010.

This new drug application provides for the use of Cuvposa (glycopyrrolate) Oral Solution to reduce chronic severe drooling in patients aged 3-16 with neurologic conditions associated with problem drooling (e.g., cerebral palsy).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)”. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **“Final Printed Carton and Container Labels for approved NDA 022571.”** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of carcinogenesis and reproductive toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1660-1 A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in mice.

The timetable you submitted on May 7, 2010 states that you will conduct this study according to the following schedule:

Study Completion Date: 07/2014  
Final Report Submission Date: 07/2015

1660-2 A 24-month oral (gavage) carcinogenicity study of glycopyrrolate in rats.

The timetable you submitted on May 7, 2010 states that you will conduct this study according to the following schedule:

Study Completion Date: 07/2014  
Final Report Submission Date: 07/2015

1660-3 Oral (gavage) fertility and general reproduction toxicity study of glycopyrrolate in rats using appropriate dose ranging.

The timetable you submitted on May 7, 2010 states that you will conduct this study according to the following schedule:

Study Completion Date: 02/2012  
Final Report Submission Date: 05/2012

1660-4 Oral (stomach tube) developmental toxicity study of glycopyrrolate in rabbits using appropriate dose ranging.

The timetable you submitted on May 7, 2010 states that you will conduct this study according to the following schedule:

Study Completion Date: 07/2013  
Final Report Submission Date: 09/2013

1660-5 Oral (gavage) developmental toxicity study of glycopyrrolate in rats using appropriate dose ranging.

The timetable you submitted on May 7, 2010 states that you will conduct this study according to the following schedule:

Study Completion Date: 10/2013  
Final Report Submission Date: 12/2013

1660-6 Oral (gavage) developmental and perinatal/postnatal reproduction toxicity study of glycopyrrolate in rats, including a postnatal behavioral/functional evaluation using appropriate dose ranging.

The timetable you submitted on May 7, 2010 states that you will conduct this study according to the following schedule:

Study Completion Date: 11/2014

Final Report Submission Date: 03/2015

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

## **LETTERS TO HEALTH CARE PROFESSIONALS**

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch  
Food and Drug Administration  
Suite 12B-05  
5600 Fishers Lane  
Rockville, MD 20857

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

## **ENCLOSURES:**

Content of Labeling  
Carton and Container 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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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SUSAN J WALKER  
07/28/2010