CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204078Orig1s000

Trade Name: Bloxiverz

Generic Name: Neostigmine Methylsulfate Injection

Sponsor: Eclat Pharmaceuticals

Approval Date: May 31, 2013

Indications: Indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery (1)

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204078Orig1s000

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APPLICATION NUMBER:

204078Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204078

NDA APPROVAL

Eclat Pharmaceuticals, LLC
c/o The Weinberg Group Inc.,
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Attention: Marla E. Scarola, MS
Senior Consultant

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated July 31, 2012, received July 31, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bloxiverz (Neostigmine Methylsulfate Injection, USP) 0.5 mg/mL and 1.0 mg/mL.

We acknowledge receipt of your amendments dated August 1 and 23, September 13 and 24, November 15 and 30, and December 28, 2012, and January 18 and 21, February 7, 13(2), and 21, March 7 and 18, April 1, 10, 22, and 30, and May 2, 6, 8, 28, and 31, 2013.

We also acknowledge receipt of your email dated May 31, 2013, that included agreed upon labeling.

This new drug application provides for the use of Bloxiverz (Neostigmine Methylsulfate Injection) for reversal of the effects of non-depolarizing neuromuscular-blocking agents (NMBAs) after surgery.

We have completed our review of this application, as amended, and 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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As,* available 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 immediate-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 *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* 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 204078**." 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.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Allison Meyer
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3176
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

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 assess a signal of a serious risk of reproductive and developmental or genotoxic potential.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk of reproductive and developmental genotoxic potential.

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

2046-1 Conduct an in vitro chromosomal aberration assay using Chinese hamster ovary cells to evaluate the potential for neostigmine to produce chromosomal damage.

The timetable you submitted on April 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	02/2014
Final Report Submission:	05/2014

2046-2 Conduct an in vivo mouse micronucleus assay for chromosomal damage for neostigmine methylsulfate.

The timetable you submitted on April 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2013
Study Completion:	02/2014
Final Report Submission:	05/2014

2046-3 Conduct a fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate.

The timetable you submitted on April 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2014
Study Completion:	03/2015
Final Report Submission:	12/2015

2046-4 Conduct an embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate.

The timetable you submitted on April 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2014
Study Completion:	10/2014
Final Report Submission:	08/2015

2046-5 Conduct an embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate.

The timetable you submitted on April 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2014
Study Completion:	01/2015
Final Report Submission:	11/2015

2046-6 Conduct a peri- and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate.

The timetable you submitted on April 30, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2014
Study Completion:	12/2015
Final Report Submission:	12/2016

Submit the protocol(s) to your IND 111853, 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 21 CFR 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
Office of Prescription Drug Promotion
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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

EXPIRY DATING PERIOD

A 24-month expiry dating period is granted for Bloxiverz (Neostigmine Methylsulfate Injection, USP) 0.5 mg/mL and 1.0 mg/mL when stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

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 Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RIGOBERTO A ROCA
05/31/2013