DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 212319

NDA APPROVAL

RAFA Laboratories LTD
c/o Doris Snow, PhD, US Agent
Vice President, Global Regulatory Affairs
Ology Bioservices
13200 Northwest Nano Court
Alachua, FL 32615

Dear Dr. Snow:

Please refer to your New Drug Application (NDA) dated and received June 27, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Atropine Injection, 2 mg/0.7 mL, Single-Dose Autoinjector.

This new drug application provides for the use of the 2 mg Atropine autoinjector for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides in adults and pediatric patients weighing over 90 lbs [41 kg] (generally over 10 years of age).

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 and with the following minor editorial revision listed below that you have agreed to implement.

- Correct the NDC number on the 480-count carton by removing the trailing zero and display the NDC number in the official FDA hyphenated format; *NDC XXXXX-XXX-XX*.

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 prescribing information, text for the information for use). 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, except with the revisions listed above, 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 212319**." Approval of this submission by FDA is not required before the labeling is used.

PHYSICIAN LABELING RULE/PREGNANCY AND LACTATION LABELING RULE

We are deferring implementation of the Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements for your labeling. Please submit a prior approval labeling supplement no later than six months of the date of this letter that proposes updates to the atropine autoinjector labeling to meet the PLR/PLLR requirements as established in 21 CFR 201.56(d) and 201.57.

PRODUCT QUALITY

Per the May 18, 2018, method validation report submitted to your cross-referenced application for the drug product assay and related substances method (Attachment 3.2.P.5.3-8), the precision of the method for (b) (4)-related impurities was not determined because all impurities were below the detection limit. Therefore, we consider the test acceptable as a limit test. If you seek to use the (b) (4)-related substances test as a quantitative measure, you may submit a supplement providing results from validation of the method using samples spiked with (b) (4)-related substances to support the switch from a limit test to a quantitative test.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 none of these criteria apply to your application, 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 unexpected serious risks of failure of the device to reliably perform and an unexpected serious risk of intended users being unable to complete the critical task of cap removal.

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.

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

3446-1 Develop reliability requirement(s) and specification(s) to mitigate the failure to fire risk, provide evidence to verify and validate the reliability specification(s), and control the reliability of the Atropine autoinjector through design and manufacturing.

In a July 2, 2018 teleconference, you agreed to conduct this study according to the following schedule:

Draft Protocol Submission:	07/2018
Final Protocol Submission:	08/2018
Study Completion:	11/2018
Final Report Submission:	01/2019

3446-2 Conduct a human factors (HF) validation study that assesses the critical task of removal of the yellow cap. This study should be conducted with 15 representative users. The users should be outfitted with dress and gear that is representative of what they would wear in a real-life scenario. Submit the human factors validation study protocol for FDA review and agreement prior to commencing the study.

In a July 2, 2018 teleconference, you agreed to conduct this study according to the following schedule:

Draft HF Validation Protocol Submission:	11/2018
Final HF Validation Protocol Submission:	01/2019
HF Validation Study Completion:	04/2019
Final HF Validation Study Report Submission:	07/2019

Postmarketing requirement (PMR) protocols and protocol-related correspondence are submitted to an IND for tracking purposes and, for PMRs involving applicable clinical trials, in accordance with the regulatory requirements under 21 CFR 312. Because our records indicate that you do not have an IND for the product referenced in this letter, we request that you submit an IND to facilitate your submissions. This IND will be opened to identify and track all applicable protocol submissions for these PMRs. The IND should include a cover letter that cross-references your NDA, and that indicates the trials will be conducted outside the U.S. You may cross-reference information from your NDA to fulfill any applicable requirements for your IND.

Submit clinical protocol(s) to your IND with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3446-3 Confirmation of Drug Product Shelf Life

In a July 2, 2018, teleconference, you agreed to conduct this study according to the following schedule:

Final Protocol Submission:	08/2018
Study Completion:	01/2019
Final Report Submission:	04/2019
Interim Report Submission:	03/2019

Postmarketing commitment (PMC) protocols and protocol-related correspondence are submitted to an IND for tracking purposes, in accordance with the regulatory requirements under 21 CFR 312. Because our records indicate that you do not have an IND for the product referenced in this letter, we request that you submit an IND to facilitate your submissions. This IND will be opened to identify and track all applicable protocol submissions for this PMC. The IND should include a cover letter that cross-references your NDA, and that indicates the trials will be conducted outside the U.S. You may cross-reference information from your NDA to fulfill any applicable requirements for your IND.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

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 prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

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 Harold Sano, Regulatory Project Manager, at (301) 301-796-2429.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labels

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM H Dunn
07/09/2018